Anticonvulsants
Therapeutic Class Review (TCR)

March 5, 2019

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Magellan Rx MANAGEMENT℠

FDA-APPROVED INDICATIONS

Drug	Manufacturer	Seizure Disorders				Neuropathic Pain	Lennox-Gastaut Syndrome	Migraine Prophylaxis	Bipolar Disorder
		Absence	Myoclonic	Partial	Tonic-Clonic				
Barbiturates									
primidone (Mysoline®)[1]	generic, Valeant			X*	X*				
phenobarbital[2]	generic		X	X*	X*				
Hydantoins									
ethotoin (Peganone®)[3]	Recordati			X*	X*				
phenytoin ER (Dilantin®)[4]	generic, Pfizer			X*	X*				
phenytoin ER (Phenytek®)[5]	generic, Mylan								
Succinimides									
ethosuximide (Zarontin®)[6]	generic, Pfizer	X*							
methsuximide (Celontin®)[7]	Pfizer	X*							
Benzodiazepines									
clobazam (Onfi®)[8]	generic, Lundbeck						X*†		
clobazam film (Sympazan™)‡ [9]	Aquestive						X*†		
clonazepam (Klonopin®)[10]	generic, Roche	X*	X*				X*		
diazepam rectal gel (Diastat®)[11]	generic, Valeant			X*†	X*†				
Carbamazepine Derivatives									
carbamazepine (Tegretol®)[12,13]	generic, Teva, Novartis			X*	X*	X (associated with trigeminal neuralgia)			
carbamazepine extended-release (Tegretol® XR)[14]	generic, Novartis								
carbamazepine extended-release (Carbatrol®)[15]	generic, Shire								

* Adult and pediatric indication

† Indicates approval for adjuvant therapy only

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FDA-Approved Indications (continued)

Drug	Manufacturer	Seizure Disorders				Neuropathic Pain	Lennox-Gastaut Syndrome	Migraine Prophylaxis	Bipolar Disorder
		Absence	Myoclonic	Partial	Tonic-Clonic				
Carbamazepine Derivatives *(continued)*									
carbamazepine extended-release (Equetro®)[16]	Validus			X*	X*	X (associated with trigeminal neuralgia)			X
eslicarbazepine (Aptiom®)[17]	Sunovion			X*					
oxcarbazepine (Trileptal®)[18]	generic, Novartis			X*					
oxcarbazepine extended-release (Oxtellar XR®)[19]	Supernus			X*					
Valproic Acid and Derivatives									
divalproex delayed-release (Depakote®)[20]	generic, Abbvie	X*	X	X	X			X	X
divalproex sodium extended-release (Depakote ER®)[21]	generic, Abbvie	X*		X*				X	X
valproic acid (Depakene®)[22]	generic, Abbvie	X*	X*	X*	X*				
Other Anticonvulsants									
brivaracetam (Briviact®)[23]	UCB			X*					

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FDA-Approved Indications (continued)

Drug	Manufacturer	Seizure Disorders				Neuropathic Pain	Lennox-Gastaut Syndrome	Migraine Prophylaxis	Bipolar Disorder
		Absence	Myoclonic	Partial	Tonic-Clonic				
Other Anticonvulsants *(continued)*									
cannabidiol (Epidiolex®)[24]	Greenwich Biosciences						X*		
felbamate (Felbatol®)[25]	generic, Meda			X*§			X†		
gabapentin (Neurontin®)[26]	generic, Pfizer			X*†		X (post herpetic neuralgia [PHN])			
lacosamide (Vimpat®)[27]	UCB			X*					
lamotrigine (Lamictal®, Lamictal® ODT)[28]	generic, GSK			X*	X*†		X*†		X‖
lamotrigine XR (Lamictal® XR)[29]	generic, GSK			X*†	X*				
levetiracetam (Keppra®)[30]	generic, UCB, OWP		X*†	X*†	X*†				
levetiracetam (Spritam®)[31]	Aprecia		X*†	X*†	X*†				
levetiracetam XR (Keppra XR®)[32]	generic, UCB, OWP			X*†					
perampanel (Fycompa®)[33]	Eisai			X*	X†*				
pregabalin (Lyrica®)[34]	Pfizer			X*†		X (associated with diabetic peripheral neuropathy, spinal cord injury, or PHN)			
rufinamide (Banzel®)[35]	Eisai						X*†		

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§ Felbamate (Felbatol) is not indicated as first-line antiepileptic treatment and is recommended for use only in patients who respond inadequately to alternative treatments and whose epilepsy is so severe that a substantial risk of aplastic anemia and/or liver failure is deemed acceptable in relation to benefits.

‖ Lamotrigine (Lamictal) is not recommended for the treatment of acute manic or mixed episodes. The effectiveness of lamotrigine has not been established for the acute treatment of mood episodes.

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FDA-Approved Indications (continued)

Drug	Manufacturer	Seizure Disorders				Neuropathic Pain	Lennox-Gastaut Syndrome	Migraine Prophylaxis	Bipolar Disorder
		Absence	Myoclonic	Partial	Tonic-clonic				
Other Anticonvulsants (*continued*)									
tiagabine (Gabitril®)[36]	generic, Cephalon			X*†					
topiramate (Topamax®)[37]	generic, Janssen			X*	X*		X*†	X*	
topiramate XR (Qudexy® XR)[38]	Upsher-Smith**			X*†	X*†		X†	X*	
topiramate XR (Trokendi XR®)[39]	Supernus			X*	X*		X*†	X*	
vigabatrin (Sabril®)[40]	generic, Lundbeck			X*†					
zonisamide (Zonegran®)[41]	generic, Concordia			X*†					

* Adult and pediatric indication

† Indicates approval for adjuvant therapy only

‡ Clobazam oral film (Sympazan) was approved under the FDA's 505(b)(2) pathway that allows at least some of the information submitted for approval to be from studies not conducted by or for the applicant.[42,43]

** Upsher-Smith manufactures brand Qudexy XR and an authorized generic version of the product.

Perampanel (Fycompa) is a Schedule III controlled substance, the barbiturates and benzodiazepines are Schedule IV; cannabidiol (Epidiolex), lacosamide (Vimpat), pregabalin (Lyrica), and brivaracetam (Briviact) are Schedule V.

Pregabalin ER (Lyrica CR) was approved in 2018 for the treatment of neuropathic pain associated with diabetic peripheral neuropathy and for post-herpetic neuralgia. It is, however, not indicated to treat seizure disorders and will not be discussed in this class review.

Other Indications:

Phenobarbital is indicated as a sedative for the relief of anxiety, tension, and apprehension. Phenobarbital is indicated for insomnia, although the barbiturates are no longer used for this indication. Phenobarbital is also indicated for treatment of status epilepticus; however, its full antiepileptic effect is not immediate. Intravenous benzodiazepines should be given initially for status epilepticus. **Note:** Phenobarbital has not been found by the FDA to be safe and effective.[44]

Phenytoin (Dilantin, Phenytek) is indicated for prevention and treatment of seizures occurring during or following neurosurgery.

Clonazepam (Klonopin) is indicated for panic disorder.

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Diazepam rectal gel (Diastat) is indicated for the management of selected, refractory patients on stable regimens of anti-epileptic agents who require intermittent use of diazepam to control bouts of increased seizure activity.

Pregabalin (Lyrica) is also indicated for treatment of fibromyalgia. Vigabatrin (Sabril) is also indicated for the treatment of infantile spasms. Carbamazepine (Equetro) is also approved for mixed-type seizures.

Cannabidiol solution (Epidiolex) is also approved for the treatment of seizures associated with Dravet syndrome in patients ≥ 2 years of age.

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OVERVIEW

Epilepsy/Seizure Disorders

Epilepsy is one of the most common disorders of the central nervous system (CNS). It affects 2.2 million Americans, with 150,000 new cases diagnosed each year.[45] When a person has 2 or more seizures, they are considered to have epilepsy. Although epilepsy can develop at any age, is the incidence is estimated to be 0.6% from birth to age 17 years and 3% at age 75 years.[46] Isolated seizures may also occur during a febrile illness, after head trauma, or as a result of withdrawal from alcohol or sedative/hypnotics.

A seizure is traceable to an unstable cell membrane or cluster of cells. Excessive excitability spreads either locally (partial seizure) or more widely (generalized seizure). Partial seizures begin in 1 hemisphere of the brain and, unless they become secondarily generalized, they can cause alterations in motor functioning, sensory symptoms, or automatisms. If there is no loss of consciousness, they are called simple partial. If there is loss or impairment of consciousness, they are called complex partial.

In 2017, the International League Against Epilepsy (ILAE) revised seizure classifications.[47,48] The new classification is based on 3 key features: seizure origin in the brain, level of awareness during the seizure, and other seizure features. The type of seizure onset will help determine the choice of anti-seizure medication, and the level of awareness can impact patient safety. Generalized seizures, previously called primary generalized, involves both sides of the brain at onset and may involve cortical and subcortical structures. Focal seizures originate on 1 side of the brain. Focal seizures may be localized or more widely distributed. Seizures that start on 1 side or area of the brain and spreads to both sides are classified as focal to bilateral seizures (previously called secondary generalized seizure). In addition, area of onset of some seizure types may not be evident; these are referred to as unknown onset seizures. Generalized onset seizures affect patient awareness. Focal onset seizures may or may not affect awareness, and are further broken down as “aware” and “impaired awareness.” In some cases, it may not be possible to determine the patients level of awareness, and, therefore, the term of awareness may considered as “awareness unknown” or not used. The ILAE classification system also describes movement and other symptoms and applies to generalized, focal, and unknown onset seizures. A seizure is described as non-motor if other symptoms, such as changes in sensation, emotions, and thinking occur. The generalized tonic-clonic seizure term is still used to describe seizures with stiffening (tonic) and jerking (clonic). Absence seizures are generalized non-motor seizures involving brief changes in awareness, staring, and repeated movements. Terms that the ILAE no longer use include complex partial, simple partial, partial, psychic, dyscognitive, and secondarily generalized tonic-clonic.

Lennox-Gastaut syndrome is one of the most severe forms of childhood epilepsy and is one of the hardest forms to treat. It is characterized by mental retardation and multiple seizure types. Patients have seizures daily, sometimes experiencing several seizures within a day. Patients may also experience “drop attacks”, which is defined as a loss of muscle control causing the patient to fall abruptly to the floor.

Dravet syndrome is a rare, catastrophic form of epilepsy that presents in the first year of life and is characterized by frequent, prolonged seizures.[49,50] Patients may experience multiple seizures types during their lifetime. Infants with Dravet syndrome often experience multiple comorbidities over their lifetime related to the persistent seizure activity including behavioral and developmental delay. Dravet

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syndrome is also associated with a 15% to 20% mortality rate due to Sudden Unexpected Death in Epilepsy (SUDEP).

Infantile spasm is a type of seizure seen in West Syndrome.[51] Infantile spasms primarily consist of a sudden bending forward of the body with stiffening of the arms and legs; some children arch their backs as they extend their arms and legs. West Syndrome is characterized by infantile spasms, developmental regression, and a specific pattern on electroencephalography (EEG) testing called hypsarrhythmia (chaotic brain waves). The onset of infantile spasms is usually in the first year of life, typically between 4 and 8 months. Infantile spasms usually stop by age 5, but may be replaced by other seizure types. Many underlying disorders can cause spasms, making it important to identify the underlying cause.

Goals of treating epilepsy are to reduce the frequency of seizure occurrence along with providing the best possible quality of life for the patient. Ideally, this would be achieved using a medication with minimal adverse effects and drug interactions. Treatment will depend on the type of seizure. Many different classes of drugs are available to treat the different forms of seizures.[52] Some patients will require more than 1 drug to control their seizures.

Previous standard guidelines were not designed to identify superior agents due to lack of comparative data. This was the recurring theme in an attempt by the ILAE to develop treatment guidelines in 2013.[53] In 2018, the American Epilepsy Society (AES) and the American Academy of Neurology (AAN) updated the 2004 evidence-based guidelines to help healthcare professionals better understand the published research on anticonvulsant agents.[54,55] The guidelines summarize the use of the newer agents at the time in patients newly diagnosed with seizures, patients with refractory seizures, and patients with refractory epilepsy. The guidelines suggest that lamotrigine (Lamictal; Level B), levetiracetam (Keppra; Level C), and zonisamide (Zonegran; Level C) may be considered for adult patients with new-onset focal epilepsy. Lamotrigine (Level B) should and gabapentin (Level C) may be considered in adults 60 years of age and older with new-onset focal epilepsy. Ethosuximide and valproic acid should be considered prior to lamotrigine in childhood absence epilepsy, unless there are concerns for adverse effects (Level B). The updated guidelines also address recommendations for treatment-resistant epilepsy. Immediate-release pregabalin (Lyrica) and perampanel (Fycompa) are recommended as first-line treatment and vigabatrin (Sabril) and rufinamide (Banzel) as second-line treatment for adults with treatment-resistant focal epilepsy (Level A). Lacosamide (Vimpat), eslicarbazepine (Aptiom), and extended-release topiramate should be considered for this population (Level B). Rufinamide (Banzel) is recommended as add-on therapy for adults with Lennox-Gastaut syndrome (Level A). Immediate- and extended-release lamotrigine should be considered for adult patients with treatment-resistant generalized tonic-clonic seizures (Level B). Levetiracetam (Keppra) has a role as adjunctive therapy in treatment-resistant childhood focal epilepsy, generalized tonic-clonic seizures, and juvenile myoclonic epilepsy (Level B). Clobazam (Onfi, Sympazan) should be considered as add-on therapy for Lennox-Gastaut therapy (Level B). Zonisamide (Zonegran) should be considered for patients aged 6 to 17 years and oxcarbazepine for patients aged 1 month to 4 years with treatment resistant childhood focal epilepsy (Level B).

The AAN and the AES released evidence-based guidelines on the prognosis and treatment of a first unprovoked seizure in adults.[56] Compared to delaying treatment until after the occurrence of a second seizure, immediate anti-epileptic (AED) drug therapy is likely to reduce the risk of recurrence within the first 2 years; however, it may not be associated with an improvement in the quality of life. Over a

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longer term period (> 3 years), immediate AED treatment is unlikely to improve the prognosis for sustained seizure remission. The guideline does not differentiate between AED treatment options.

The AAN and the Child Neurology Society recommend low-dose adrenocorticotropic hormone (ACTH) as the treatment of choice for infantile spasms.[57] ACTH or vigabatrin (Sabril) may be useful for short-term treatment, with ACTH preferred. The Task Force Report for the ILAE Commission of Pediatrics also supports the use of ACTH for short-term control of epileptic spasms.[58] There is insufficient evidence that other anticonvulsants and combination therapy are effective for short-term treatment. In infants with cryptogenic infantile spasms, ACTH or prednisolone may be considered for use in preference to vigabatrin, as ACTH and prednisolone may result in improved developmental outcomes. A shorter lag time to treatment of infantile spasms with either hormonal therapy or vigabatrin also possibly improves long-term developmental outcomes.

The AAN and the AES released an evidence-based guideline for the treatment of convulsive status epilepticus in children and adults.[59] Status epilepticus is traditionally defined as > 30 minutes of continuous seizure activity or 2 or more sequential seizures without full recovery of consciousness in between. In addition to the traditional definition of status epilepticus, the ANN/AES guidance also considers any seizure lasting > 5 minutes to be prolonged and therefore included in the guideline. Intramuscular (IM) midazolam and intravenous (IV) lorazepam, diazepam, and phenobarbital are efficacious in adults with convulsive status epilepticus (Level A). In children, IV lorazepam and diazepam are effective at stopping seizures lasting at least 5 minutes (Level A), while rectal diazepam and midazolam (IM, intranasal, and buccal) are probably effective (Level B). For both adults and children, there was no significant difference in efficacy between IV lorazepam and IV diazepam (Level A).

In 2017, the AAN and AES created guidelines regarding sudden unexpected death in epilepsy (SUDEP).[60] Based on 12 Class I studies, they found that the yearly incidence of SUDEP was about 1/4,500 in children and 1/1,000 in adults. The most notable risk factor was generalized tonic-clonic seizures (GTCS), which was found to be the precipitating event of SUDEP, and is of particular concern in patients who experience at least 3 tonic-clonic seizures per year. Physicians should communicate these risks to all epileptic patients and their caregivers and should actively manage epilepsy therapies to reduce seizure occurrences while considering patient preferences and the risks and benefits of any new approach.

About 70% of patients with epilepsy can be maintained on 1 drug.[61] Noncompliance and evolving refractory epilepsy are common reasons for treatment failure.[62] If control is not achieved with 1 drug, an alternative medication should be attempted before others are added to current therapy.

Bipolar Disorder

Bipolar disorder is characterized by episodes of mania, depression, or a mixed state. Criterion used to diagnose Bipolar I Disorder are the presence of a manic episode (persistent elevated, expansive, or irritable mood for at least 1 week with increased energy/activity) or a mixed features specifier (rapidly alternating polarity of mood, sadness, irritability, and mania for at least 1 week), and ≥ 3 other characteristic symptoms are present.[63,64] These symptoms include inflated self-esteem or grandiosity, decreased need for sleep, more talkative than usual or pressured speech, flight of ideas or feelings of racing thoughts, distractibility, increase in goal-directed activity or psychomotor agitation, and excessive involvement in risky pleasurable activities. The hallmark of a true manic episode include

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symptoms severe enough to cause significant impairment in functioning, requires hospitalization to prevent harm to self or others, and the presence of psychotic features.

Criterion used to diagnose a Bipolar II Disorder includes 1 or more depressive episodes nearly every day during the same 2-week period with at least 1 hypomanic episode lasting at least 4 days.[65] The depressive episodes are marked by the appearance of 5 or more depressed symptoms, which include a depressed mood most of the day every day, diminished interest in activities and hobbies, significant weight change, insomnia or hypersomnia, psychomotor agitation or retardation nearly every day, fatigue, feeling of guilt or worthlessness, indecisiveness or inability to concentrate, and recurrent thoughts of death or suicide. Hypomanic episodes are defined as a persistently elevated, expansive, or irritable mood with increased energy/activity and 3 or more other symptoms. These symptoms include inflated self-esteem, decreased need for sleep, pressured speech, distractibility, increase in goal-directed behavior, and excessive involvement with risky activities. The diagnosis of hypomania is very similar to mania, but the episodes do not result in significant impairment of functioning, they do not necessitate hospitalization, and no psychotic symptoms are present.

A few anticonvulsants have been approved by the Food and Drug Administration (FDA) for the treatment of bipolar disorder, while others have been used off-label to treat the condition. Carbamazepine (Equetro), an extended-release formulation, is indicated for treatment of acute manic and mixed episodes associated with bipolar I disorder. Lamotrigine (Lamictal) is also approved for maintenance of bipolar I disorder, although not for the treatment of acute manic or mixed episodes. Several valproic acid derivatives are approved for management of bipolar disorder including divalproex (Depakote) and divalproex ER (Depakote ER).

The American Psychiatric Association (APA) guidelines on bipolar disorder recommend either lithium or valproate plus an antipsychotic medication as first-line for patients with severe mania; monotherapy may be considered in less severe patients.[66] Regarding episodes of bipolar depression, initiation of lithium or lamotrigine is recommended as first-line treatment. In patients who experience rapid cycling, lithium or valproate are recommended, with lamotrigine considered as an alternative. Lithium and valproate have the best empirical evidence to support their use for maintenance treatment of bipolar disorder; lamotrigine, carbamazepine, and oxcarbazepine are possible alternatives.

Prevention of Migraine

Migraine headache prophylaxis has been suggested for patients whose headaches occur in a predictable pattern (menstrual migraine), occur more than 2 to 3 times per month, are intolerable or produce profound impairment, and when symptomatic therapies have failed to provide relief or produced serious adverse effects.[67] A 2000 evidence-based practice guideline by the AANs Quality Standards Subcommittee recommends that preventive therapy goals include: reduced migraine frequency, severity, duration, and disability and improved responsiveness to treatment of acute attacks and function.[68] The 2012 AAN/American Headache Society (AHS) pharmacologic treatment guidelines for episodic migraine prevention in adults recommend the following FDA-approved agents as effective treatment: divalproex sodium, sodium valproate, topiramate, and the beta-blockers metoprolol, timolol, and propranolol.[69] Several other agents are FDA-approved for the prevention of migraine, including onabotulinumtoxinA (Botox®), erenumab-aooe (Aimovig™), fremanezumab-vfrm (Ajovy™), and galcanezumab-gnlm (Emgality®). In 2019, the American Headache Society (AHS) released a position statement on integrating select new migraine treatments into clinical practice

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Drug	Mechanism of Action
Barbiturates	
primidone (Mysoline)	Barbiturates depress CNS activity by binding to the barbiturate site at the gamma-aminobutyric acid (GABA) receptor complex, enhancing GABA activity Barbiturates reduce monosynaptic and polysynaptic transmission resulting in decreased excitability of the entire nerve cell; they also increase the threshold for electrical stimulation of the motor cortex
phenobarbital	
Hydantoins	
ethotoin (Peganone)	The hydantoins appear to stabilize rather than raise the seizure threshold and prevent the spread of seizure activity rather than abolish the primary focus of discharge. The primary site of action appears to be the motor cortex; possibly by promoting sodium efflux from neurons, hydantoins tend to stabilize the threshold against hyperexcitability caused by excessive stimulation or environmental changes capable of reducing membrane sodium gradient
Phenytoin (Dilantin, Phenytek)	
Succinimides	
ethosuximide (Zarontin)	Succinimides suppress the paroxysmal 3-cycles-per-second spike and wave activity associated with lapses of consciousness common in absence seizures; the frequency of epileptiform attacks is reduced, apparently by motor cortex depression and elevation of the threshold of the CNS to convulsive stimuli
methsuximide (Celontin)	
Benzodiazepines	
clobazam (Onfi, Sympazan)	Benzodiazepines potentiate the effects of GABA; benzodiazepines suppress the spike and wave discharge associated with absence seizures
clonazepam (Klonopin)	
diazepam rectal gel (Diastat)	
Carbamazepine Derivatives	
carbamazepine (Tegretol, Tegretol XR, Carbatrol, Epitol, Equetro)	Carbamazepine reduces polysynaptic responses and blocks the post-tetanic potentiation; the mechanism of action of carbamazepine in bipolar disorder and treatment of pain in trigeminal neuralgia is unknown
eslicarbazepine acetate (Aptiom)	Eslicarbazepine is a voltage-gated sodium channel (VGSC) blocker that inhibit sustained repetitive neuronal firing; eslicarbazepine has a much higher affinity for the inactivated state of VGSC than the resting state, suggesting an enhanced inhibitory selectivity for rapidly firing neurons over those displaying normal activity
oxcarbazepine (Trileptal, Oxtellar XR)	*In vitro* electrophysiological studies indicate that oxcarbazepine blocks voltage-sensitive sodium channels, resulting in stabilization of hyperexcited neural membranes, inhibition of repetitive neuronal firing, and diminishes propagation of synaptic impulses
Valproic Acid And Derivatives	
valproic acid (Depakene) divalproex (Depakote, Depakote ER, Depakote Sprinkle)	Valproic acid and derivatives increase brain concentration of GABA, an inhibitory neurotransmitter of the CNS

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Pharmacology (continued)

Drug	Mechanism of Action
Other Anticonvulsants	
brivaracetam (Briviact)	Mechanism unknown; it has highly selective and reversible affinity for synaptic vesicle protein 2A (SV2A) in the brain and also modulates the voltage-dependent sodium channels
cannabidiol (Epidiolex)	Mechanism unknown; anticonvulsant properties are not due to interaction with cannabinoid receptors
felbamate (Felbatol)	*In vitro* studies indicate felbamate has weak inhibitory effects on GABA-receptor binding and benzodiazepine receptor binding
gabapentin (Neurontin)	Gabapentin increases GABA synthesis; it binds to the presynaptic α_2-delta subunit of voltage sensitive calcium channels
lacosamide (Vimpat)	Lacosamide selectively enhances slow inactivation of voltage-gated sodium channels, resulting in stabilization of hyperexcitable neuronal membranes and inhibition of repetitive neuronal firing
lamotrigine (Lamictal, Lamictal XR)	Lamotrigine inhibits voltage-sensitive sodium channels, thereby stabilizing neuronal membranes which modulate presynaptic transmitter release of excitatory amino acids
levetiracetam (Keppra, Keppra XR, Spritam)	Modulates synaptic neurotransmitter release through binding to the synaptic vesicle protein SV2A in the brain
perampanel (Fycompa)	Perampanel is a non-competitive antagonist of the ionotropic AMPA glutamate receptor on postsynaptic neurons
pregabalin (Lyrica)	Pregabalin binds to presynaptic α_2-delta subunit of voltage sensitive calcium channels, inhibiting release of pro-nociceptive neurotransmitters in the spinal cord
rufinamide (Banzel)	*In vitro* studies indicate rufinamide modulates the activity of the sodium channels by prolonging the inactivity of the channel
tiagabine (Gabitril)	Tiagabine enhances the activity of GABA
topiramate (Topamax, Qudexy XR, Trokendi XR)	Topiramate exhibits sodium channel blocking action; potentiates activity of GABA; antagonizes the glutamate (excitatory amino acid) receptor; and inhibits carbonic anhydrase
vigabatrin (Sabril)	Irreversibly inhibits γ-aminobutyric acid transaminase (GABA-T), the enzyme responsible for the metabolism of the inhibitory neurotransmitter GABA; this action results in increased levels of GABA in the CNS
zonisamide (Zonegran)	Zonisamide blocks sodium channels and reduces voltage-dependent, transient, inward currents, consequently stabilizing neuronal membranes and suppressing neuronal hypersynchronization; it also facilitates both dopaminergic and serotonergic transmission and is a weak carbonic anhydrase inhibitor

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Drug	Half-Life (hr)	Active Metabolites	Excretion (%)	Therapeutic Serum Levels (µG/mL)
Barbiturates				
primidone (Mysoline)	10-12	PEMA (half-life 29-36 hours) phenobarbital (half-life 53-140 hours)	Renal: 64	5-12 15-40
phenobarbital	53-140	--	Urine: 25	15-40
Hydantoins				
ethotoin (Peganone)	3-9	3	Metabolites Urine	15-50
phenytoin (Dilantin, Phenytek)	7-42	No	After reabsorption from intestinal track- Urine	10-20
Succinimides				
ethosuximide (Zarontin)	60 (adults) 30 (children)	No	Parent unchanged 12-20 metabolites 40-60 Renal	40-100
methsuximide (Celontin)	2.6-4	N-desmethyl-methsuximide (NDM)	--	--
Benzodiazepines				
clobazam (Onfi, Sympazan)	36-42	N-desmethylclobazam (half-life 71-82 hours)	Urine: 2 Feces: 1	--
clonazepam (Klonopin)	30-40	No	Metabolites Urine	20-80 ng/mL
diazepam rectal gel (Diastat)	46	desmethyldiazepam (half-life 71 hours) 3-hydroxydiazepam 3-hydroxy-N-diazepam	Metabolites Urine	--
Carbamazepine Derivatives				
carbamazepine (Tegretol, Tegretol XR, Carbatrol, Epitol, Equetro)	25-65 initially then 12-17 after repeated doses	10,11-epoxide	Metabolites Urine: 72 Feces: 28	4-12
eslicarbazepine acetate (Aptiom)	13-20	eslicarbazepine	Renal: 60 Metabolites Urine: 40	--

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Pharmacokinetics (continued)

Drug	Half-Life (hr)	Active Metabolites	Excretion (%)	Therapeutic Serum Levels (mcg/mL)
Carbamazepine Derivatives (*continued*)				
oxcarbazepine (Trileptal)	2	10-mono-hydroxy (MHD, half-life 9 hours)	Metabolites Urine: 95 Feces: < 4	--
oxcarbazepine (Oxtellar XR)*	7-11	10-mono-hydroxy (MHD, half-life 9 hours)	Metabolites Urine: 95 Feces: < 4	--
Valproic Acid And Derivatives				
valproic acid (Depakene), divalproex sodium (Depakote, Depakote ER, Depakote Sprinkle)	9-16	Yes	Metabolites Renal	50-100
Other Anticonvulsants				
brivaracetam (Briviact)	9	No	Urine: > 95 (< 10 unchanged) Feces: < 1	--
cannabidiol (Epidiolex)	56-61	7-OH-CBD	Metabolites Feces (minor)	--
felbamate (Felbatol)	20-23	No	Metabolites Urine: > 90	--
gabapentin (Neurontin)	5-7	No	Renal	--
lacosamide (Vimpat)	13	No	Urine: 95	--
lamotrigine (Lamictal)	25	No	Urine: 94 Feces: 2	--
lamotrigine (Lamictal XR)	33	No	Urine: 94 Feces: 2	--
levetiracetam (Keppra, Keppra XR, Spritam)	6–8	No	Urine: 66 unchanged	--
perampanel (Fycompa)	105	No	Urine: 22 Feces: 48	--
pregabalin (Lyrica)	6	No	Urine: 90-98 unchanged	--
rufinamide (Banzel)	6-10	No	Urine: 85	--
tiagabine (Gabitril)	7-9	No	Metabolites Urine: 25 Metabolites Feces: 63	--

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Pharmacokinetics (continued)

Drug	Half-Life (hr)	Active Metabolites	Excretion (%)	Therapeutic Serum Levels (mcg/mL)
Other Anticonvulsants *(continued)*				
topiramate (Topamax)	21	No	Urine: 70 unchanged	--
topiramate XR (Qudexy XR)	56	No	Urine: 70 unchanged	--
topiramate XR (Trokendi XR)	31	No	Urine: 70 unchanged	--
vigabatrin (Sabril)	7.5	No	Urine 95 (80 unchanged)	--
zonisamide (Zonegran)	63	N-acetyl zonisamide SMAP	Urine: 62 (35 unchanged) Feces: 3	--

hr = hours

*At steady state, oxcarbazepine ER (Oxtellar XR) once daily produced MHD exposures (AUC and Cmax) about 19% lower and monohydroxy metabolite (MHD) minimum concentrations (Cmin) about 16% lower than IR oxcarbazepine administered at the same 1,200 mg total daily dose. When oxcarbazepine ER was administered at an equivalent 600 mg single dose equivalent MHD exposures (AUC) were observed.

CONTRAINDICATIONS/WARNINGS[153,154,155,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194]

Drug	Selected Warnings	Monitoring
barbiturates[195]	habit forming; additive CNS depression when used with other CNS depressants; contraindicated in patients with porphyria, marked impairment of liver function, or respiratory disease in which dyspnea or obstruction is evident	periodic lab evaluation of hematopoietic, hepatic, and renal systems
benzodiazepines	interference with cognitive and motor functioning; additive CNS depression when used with opioid medications	periodic blood counts and liver function tests (LFTs)
carbamazepines	serious dermatologic reactions (e.g., Steven Johnsons syndrome, especially in Han Chinese [25%] and significant levels in other southeast Asians with high proportion of Han Chinese ancestry [e.g., Bangkok Thai]); bone marrow suppression; anaphylaxis and angioedema	testing for HLA-B*1502 in patients with Asian ancestry; pretreatment blood count
hydantoins	lymphadenopathy, alcohol intake, exacerbation of porphyria, hepatic abnormalities and hematologic disorders	phenytoin serum concentrations, complete blood count (CBC), LFTs, urinalysis
succinimides	blood dyscrasias, functional liver and renal changes, systemic lupus erythematosus (SLE)	periodic blood counts, liver function testing, urinalysis

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In 2008, the FDA informed healthcare professionals that the Agency has analyzed reports of suicidality (suicidal behavior or ideation) from placebo-controlled clinical studies of 11 drugs used to treat epilepsy, as well as psychiatric disorders and other conditions.[196] In the FDA's analysis, patients receiving antiepileptic drugs had approximately twice the risk of suicidal behavior or ideation (0.43%) compared to patients receiving placebo (0.22%). The increased risk of suicidal behavior and suicidal ideation was observed as early as 1 week after starting the antiepileptic drug and continued through 24 weeks. The results were generally consistent among the 11 drugs. The relative risk for suicidality was higher in patients with epilepsy compared to patients who were given 1 of the drugs in the class for psychiatric or other conditions. The FDA advises healthcare professionals to closely monitor all patients currently taking or starting any antiepileptic drug for notable changes in behavior that could indicate the emergence or worsening of suicidal thoughts, behavior, or depression. The 11 drugs included in the analysis were carbamazepine (Carbatrol, Equetro, Tegretol, Tegretol XR), felbamate (Felbatol), gabapentin (Neurontin), lamotrigine (Lamictal), levetiracetam (Keppra), oxcarbazepine (Trileptal), pregabalin (Lyrica), tiagabine (Gabitril), topiramate (Topamax), valproate (Depakote, Depakote ER, Depakene), and zonisamide (Zonegran). Even though other products were not included in the analysis, the risk of suicidal behavior and suicidal ideation is still possible and should be monitored in patients receiving treatment. All antiepileptic drugs contain this warning.

All antiepileptic drugs should be gradually withdrawn to minimize the potential of increased seizure frequency.

In pregnancy, the use of anticonvulsants is associated with congenital malformations including craniofacial anomalies, neurological abnormalities, and congenital heart defects.[197] An observational study from the United Kingdom Epilepsy and Pregnancy Registry of 3,607 females identified the rate of congenital malformations in women using all epileptics was 4.2% versus 3.5% with untreated epilepsy. The risk was higher in those women that used polytherapy versus monotherapy, 6% versus 3.7%, respectively. Several studies have suggested that the use of valproate may have a higher risk compared to other antiepileptics.[198,199,200] Divalproex sodium and valproic acid carry a boxed warning for fetal risk.

Benzodiazepines should not be used in patients with clinical or biochemical evidence of significant liver disease. They may be used in patients with open angle glaucoma who are receiving appropriate therapy, but are contraindicated in those with acute narrow angle glaucoma. In 2016, the FDA informed healthcare professionals that use of opioids concurrently with benzodiazepines or other CNS depressants has resulted in serious adverse reactions.[201] Providers should limit prescribing of opioids with benzodiazepines to patients without alternative treatment options. If used together, dosages and duration of therapy should be minimized. The FDA is adding Boxed Warnings to the drug labeling of all prescription opioids, including those for pain and for cough, and benzodiazepines. The FDA updated the safety warning for concurrent opioid and benzodiazepine prescribing in patients being treated for opioid use disorder. Careful medication management is recommended to reduce the risk of serious side effects when concurrent therapy is required.[202]

brivaracetam (Briviact)

Brivaracetam is contraindicated in patients with known hypersensitivity to any component of the product. Reports of hypersensitivity reactions, including bronchospasm and angioedema, have occurred with brivaracetam; discontinue if a reaction occurs.

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cannabidiol (Epidiolex)

Cannabidiol is contraindicated in patients with known hypersensitivity to cannabidiol or any of its ingredients, including sesame seed oil. Hypersensitivity reactions, including pruritus, erythema, and angioedema, were reported and required treatment with antihistamines. If a hypersensitivity reaction occurs during treatment, cannabidiol should be discontinued.

carbamazepine (Carbatrol, Equetro, Tegretol/XR, Epitol)

For carbamazepine products, serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), have been reported during treatment. These reactions are estimated to occur in 1 to 6 per 10,000 new users in countries with mainly Caucasian populations, but the risk in some Asian countries is estimated to be about 10 times higher. Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS or TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene. HLA-B*1502 is found almost exclusively in patients with ancestry across broad areas of Asia. Patients with ancestry in genetically at-risk populations should be screened for the presence of HLA-B*1502 prior to initiating treatment with carbamazepine. Patients testing positive for the allele should not be treated with carbamazepine unless the benefit clearly outweighs the risk.

There is a moderate association between the risk of developing hypersensitivity reactions, including SJS/TEN, maculopapular eruptions, and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and the presence of HLA-A*3101, an inherited allelic variant of the HLA-A gene, in patients using carbamazepine. HLA-A*3101 is carried by more than 15% of Japanese, Native American, Southern Indian, and some Arab patients; up to about 10% of Han Chinese, Korean, European, Latin American, and other Indian patients ancestry; and up to about 5% in African-Americans and patients of Thai, Taiwanese, and Chinese ancestry. Manifestations of DRESS typically include fever, rash, and/or lymphadenopathy in conjunction with other organ system abnormalities including hepatitis, nephritis, hematologic abnormalities, myocarditis, or myositis. Eosinophilia is often present.

Aplastic anemia and agranulocytosis have been reported in association with the use of carbamazepine. Data from a population-based, case-control study indicate the risk of developing these reactions is 5 to 8 times greater than in the general population; however, the overall risk of developing these reactions in the untreated general population is low. Furthermore, these reactions occur in approximately 6 patients per 1 million population per year for agranulocytosis, and 2 patients per 1 million populations per year for aplastic anemia. Even though reports of transient or persistent decreased platelet or white blood cell counts are associated with the use of carbamazepine, data are not available to accurately estimate their incidence or outcome. The majority of the reported cases of leukopenia have not progressed to the more serious conditions of aplastic anemia or agranulocytosis. Due to the very low incidence of agranulocytosis and aplastic anemia, the majority of minor hematologic changes observed while monitoring patients on carbamazepine are unlikely to signal the occurrence of either abnormality. Nonetheless, complete pretreatment hematological testing at baseline should be obtained, and monitoring should occur if the patient exhibits low or decreased white blood cell or platelet counts during treatment. Discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.

Carbamazepine should not be used in patients with a history of previous bone marrow depression, hypersensitivity to the drug, or known sensitivity to any of the tricyclic compounds, such as

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amitriptyline, desipramine, imipramine, protriptyline, and nortriptyline. Theoretically, the use of carbamazepine with monoamine oxidase (MAO) inhibitors is not recommended. Before administration of carbamazepine, MAO inhibitors should be discontinued for a minimum of 14 days or longer if the clinical situation permits. Carbamazepine should be avoided in patients with a history of hepatic porphyria (e.g., acute intermittent porphyria, variegate porphyria, porphyria cutanea tarda). Acute attacks have been reported in such patients receiving carbamazepine therapy.

Rare instances of vanishing bile duct syndrome have been reported with carbamazepine. This syndrome consists of a cholestatic process with a variable clinical course ranging from fulminant to indolent, involving the destruction and disappearance of the intrahepatic bile ducts. Some cases are associated with features of other immunoallergenic syndromes such as multi-organ hypersensitivity (DRESS syndrome) and serious dermatologic reactions, including SJS.

clobazam (Onfi, Sympazan)

Clobazam (Onfi, Sympazan) is contraindicated in patients with a history of hypersensitivity to the drug or its ingredients. Serious skin reactions, including SJS and TEN, have been reported in both children and adults. Patients should be closely monitored for signs or symptoms especially during the first 8 weeks of treatment or when re-introducing therapy.

Somnolence or sedation associated with clobazam is dose-related and reported in all effective doses but may abate after the first month of treatment. Patients should limit activities that require mental alertness until the effect of the mediation is known. Additional CNS depressants, including other medications and alcohol, may increase sedative side effects.

Tapering a benzodiazepine should occur slowly to avoid withdrawal symptoms. Withdrawal symptoms include seizure exacerbation, status epilepticus, psychosis, hallucinations, tremor, anxiety, and behavioral disorders. To minimize the risk, tapering should occur by decreasing 5 to 10 mg/day every week until discontinued. More severe withdrawal symptoms are experience by patients using higher doses or taking therapeutic doses for longer periods of time. Similar to other benzodiazepines, patients may become physically and psychological dependent on clobazam, and patients with substance abuse history should be closely monitored.

eslicarbazepine acetate (Aptiom)

Eslicarbazepine acetate is contraindicated in patients with a hypersensitivity to eslicarbazepine acetate or oxcarbazepine.

Serious dermatologic reactions, including SJS and TEN, have been reported with eslicarbazepine acetate. Both SJS and TEN have been reported in patients using oxcarbazepine or carbamazepine, which are chemically related to eslicarbazepine acetate. Patients with a prior dermatologic reaction with oxcarbazepine should not be treated with eslicarbazepine acetate.

DRESS has been reported with eslicarbazepine acetate. If evidence of hypersensitivity presents, the patient should be evaluated immediately, the product discontinued and not resumed if an alternative etiology cannot be established. Patients with a prior DRESS reaction with either oxcarbazepine or eslicarbazepine acetate should not be treated with eslicarbazepine acetate.

Clinically significant hyponatremia, defined as serum sodium level < 125 mmol/L, can develop in patients taking eslicarbazepine acetate. It is generally dose-related and usually appears in the first 8

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weeks of treatment. Sodium and chloride levels should be monitored throughout treatment. Neurological adverse reactions including dizziness, changes in coordination, somnolence, cognitive dysfunction, visual changes, and fatigue have been noted. In addition to cases of symptomatic hyponatremia, syndrome of inappropriate antidiuretic hormone (SIADH) have been reported.

Eslicarbazepine acetate also causes dose-dependent increases in visual changes including diplopia, blurred, and impaired vision. This is more common in patients older than 60 years of age or when used concomitantly with carbamazepine. There may also be dose-dependent increases in somnolence and fatigue-related adverse reactions, as well as cognitive dysfunction. Patients should not engage in hazardous activities requiring mental alertness, such as operating motor vehicles or dangerous machinery, until the effects of eslicarbazepine acetate are known.

Elevations in transaminases (> 3 times the upper limit of normal [ULN]) with concomitant elevations of total bilirubin (> 2 times the ULN) in the absence of obstruction have been reported with eslicarbazepine acetate. Baseline and periodic liver laboratory tests are recommended.

Postmarketing reports of rare cases of pancytopenia, agranulocytosis, and leukopenia have been reported. Eslicarbazepine acetate discontinuation should be considered in these cases.

felbamate (Felbatol)

Felbamate is not indicated as a first-line antiepileptic therapy. It is recommended for use only in those patients who respond inadequately to alternative treatments and whose epilepsy is so severe that the benefits of its use outweighs the substantial risk of aplastic anemia and/or liver failure conferred by its use. Among felbamate-treated patients, aplastic anemia occurs at an incidence of more than 100-fold greater than that seen in the untreated population. The clinical manifestation of aplastic anemia may not be seen until after a patient has been on felbamate for several months; however, the injury to the bone marrow stem cells that is ultimately responsible for the anemia may occur weeks to months earlier. Patients who discontinue felbamate remain at risk for developing anemia for a variable and unknown period afterwards. Felbamate should be discontinued if bone marrow suppression develops. Routine blood testing cannot be reliably used to reduce the incidence of aplastic anemia but, in some cases, it will allow for the detection of hematologic changes before the syndrome presents clinically.

Postmarketing data suggest that acute liver failure is associated with the use of felbamate. Of the reported cases, two-thirds resulted in death or liver transplantation, usually within 5 weeks of the onset of signs and symptoms of liver failure. Felbamate should be initiated only in patients without active liver disease and with normal baseline serum transaminases. Periodic serum transaminase testing may detect early drug-induced hepatic injury, but it has not been proven to prevent serious injury. Immediate withdrawal of felbamate is warranted with evidence of hepatic injury (≥ 2 times ULN for aspartate aminotransferase [AST] or alanine aminotransferase [ALT] or if clinical signs and symptoms develop). Baseline and periodic monitoring of serum transaminases (AST and ALT) are recommended. Patients are considered at an increased risk of liver injury if felbamate is reintroduced after the development of hepatocellular injury during felbamate treatment and who are withdrawn from the drug for any reason. These patients should not return to felbamate treatment. Treatment with felbamate should occur only if the criteria for normal liver function are met, the patient has been fully advised of the risk, and has provided written, informed consent. After recommended criteria are met, felbamate can be considered for either monotherapy or adjunctive therapy in adults.

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lacosamide (Vimpat)

Dose-dependent PR interval prolongation and atrioventricular block have been observed in clinical trials. Lacosamide should be used with caution in patients with known cardiac conduction problems or with severe cardiac disease, such as myocardial ischemia or heart failure. Atrial fibrillation and flutter have also been reported.

DRESS has been reported with other antiepileptics. If signs or symptoms of DRESS occur, discontinue lacosamide if an alternative cause cannot be determined.

lamotrigine (Lamictal, Lamictal XR)

Serious rashes, including SJS and TEN, requiring hospitalization and discontinuation of treatment have been reported in association with the use of lamotrigine. The incidence of these rashes, which have included SJS, is approximately 0.3% to 0.8% in pediatric patients (age < 16 years) and 0.3% in adults receiving lamotrigine as adjunctive therapy for epilepsy. Based on the labeling, the rates in children appear to be correlated with rapid dose escalations, exceeding FDA recommended dose, and concomitant use with valproate. In clinical trials of bipolar and other mood disorders, the rate of serious rash was 0.08% in adult patients receiving lamotrigine as initial monotherapy and 0.13% receiving as adjunctive therapy. Rare cases of TEN and/or rash-related death have been reported in adult and pediatric patients. Although uncertain, the co-administration of lamotrigine with valproate, exceeding the recommended initial dose of lamotrigine, or exceeding the recommended dose escalation for lamotrigine may increase the risk of rash; however, case reports have occurred in the absence of these factors. Nearly all cases of life-threatening rashes associated with lamotrigine have occurred within 2 to 8 weeks after treatment initiation. Benign rashes also occur with lamotrigine; however, it is difficult to determine which rashes will prove serious or life-threatening. Recommendations are to discontinue lamotrigine at the first sign of rash unless the rash is clearly not drug-related.

Aseptic meningitis has been reported in both children and adults receiving lamotrigine. The FDA identified 40 cases of aseptic meningitis in patients receiving lamotrigine from December 1994 to November 2009.[203] Postmarketing reports indicate that symptoms may include headache, fever, nausea, vomiting, nuchal rigidity, photophobia, myalgia, chills, altered consciousness, and somnolence. Cerebrospinal fluid analysis has shown mild to moderate pleocytosis, normal glucose concentrations, and mild to moderate increases in protein. Some patients have had an underlying autoimmune disease, such as systemic lupus erythematosus (SLE). New onset hepatic and renal involvement have occurred in some instances, which may suggest these cases were part of a hypersensitivity reaction. Aseptic meningitis associated with lamotrigine has historically developed between 1 day and 1.5 months after treatment initiation, and resolution usually occurs upon discontinuation of the drug. Re-exposure to lamotrigine can result in a rapid return of the condition (e.g., 30 minutes to 1 day) with more severe symptoms. If aseptic meningitis is suspected during the use of lamotrigine, the patient should be promptly evaluated and the underlying cause diagnosed so that the appropriate treatment can be initiated. Discontinuation of lamotrigine should be considered if no other cause can be identified. Patients receiving lamotrigine should be advised to report signs and symptoms of meningitis to their healthcare professional.

DRESS, a multi-organ hypersensitivity reaction, has occurred with lamotrigine. Early manifestations, such as fever and lymphadenopathy, may be present without evidence of a rash. Cases of isolated

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hepatic failure without rash or other organ involvement have also been reported. Three cases of multiorgan dysfunction and disseminated intravascular coagulation (DIC) occurred within 14 days of adding lamotrigine to an existing antiepileptic drug regimen, with subsequent resolution of symptoms following discontinuation of the drug. Fatalities associated with hepatic failure or multiorgan failure occurred in 2 of 3,796 adults and 4 of 2,435 pediatric patients during clinical trials. Fatalities have also been rarely reported during postmarketing use. Pruritus was reported in 2% of pediatric patients and ≥ 5% or more of adult patients during clinical trials. Maculopapular rash and urticaria were infrequently reported (0.1–1%). Angioedema, erythema, and eosinophilia occurred rarely (< 0.1%).

Lamotrigine has been reported to interfere with some rapid urine drug screens, resulting in false-positive results, particularly for phencyclidine (PCP). A more specific method should be used for confirmation of a positive result.

Hemophagocytic lymphohistiocytosis (HLH), a life-threatening syndrome of immune activation characterized by extreme systemic inflammation, has occurred in patients taking lamotrigine. Common symptoms include fever, hepatosplenomegaly, rash, lymphadenopathy, neurologic symptoms, cytopenias, abnormal liver function, and coagulopathies. These symptoms have been reported within 8 to 24 days following the initiation of lamotrigine. Lamotrigine should not be restarted if an alternative source for the symptoms cannot be determined.

levetiracetam (Keppra, Keppra XR, Spritam)

Sensitivity reactions, including anaphylaxis and angioedema, have been reported with levetiracetam. The product is contraindicated in patients with a hypersensitivity to levetiracetam.

In adults experiencing partial onset seizures, levetiracetam is associated with the occurrence of CNS adverse events that can be classified into the categories of somnolence and fatigue, coordination difficulties, and behavioral abnormalities. Somnolence, asthenia, and coordination difficulties occur most frequently within the first 4 weeks of treatment. Also, levetiracetam is associated with somnolence, fatigue, and behavioral abnormalities in pediatric patients experiencing partial onset seizures. Psychiatric abnormalities also occurred in adult studies of generalized tonic-clonic seizures and pediatric studies of partial onset seizures. Behavioral abnormalities include both psychotic and non-psychotic reactions. There is a worsening of aggressive behavior in children; 11.7% of children ages 1 month to less than 4 years have exhibited irritability. Psychosis developed in 1% of adults, 2% of children 4 to 16 years of age, and 17% of children 1 month to < 4 years of age.

Severe dermatological reactions, including SJS and TEN, have been reported in children and adults treated with levetiracetam. Usual onset is 14 to 17 days after initial treatment, but cases have been reported for patients using the medications for 16 weeks. Levetiracetam should be discontinued at the first sign of a rash, unless it can be definitively established that the rash is not due to the medication. Medication trials are not recommended after resolution of possible SJS or TEN.

Levetiracetam can cause hematologic abnormalities, including decreases in red blood cell counts, hemoglobin and hematocrit, as well as an increase in eosinophils. Reductions in white blood cell and neutrophil counts have also been seen in clinical trials. Postmarketing reports have cited cases of agranulocytosis, pancytopenia, and thrombocytopenia. Patients experiencing significant weakness, pyrexia, recurrent infections, or coagulation disorders should be assessed with a complete blood count.

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In a placebo-controlled randomized study, a significantly higher risk of increased diastolic blood pressure was observed in patients being treated with levetiracetam between the ages of 1 month and 4 years, as compared to placebo-treated patients. No differences between treatment and placebo groups were observed in patients over the age of 4 years. Patients between the ages of 1 month and 4 years should be monitored for increases in diastolic blood pressure.

oxcarbazepine/ER (Trileptal, Oxtellar XR)

Oxcarbazepine (Trileptal) is contraindicated in patients with a known hypersensitivity any of the components of the product or to eslicarbazepine acetate (Aptiom).

Patients who have had hypersensitivity reactions to carbamazepine should be informed that approximately 25% to 30% will experience hypersensitivity reactions with oxcarbazepine. For this reason, a thorough history of hypersensitivity reactions with carbamazepine should be obtained prior to treatment, and patients with a positive history should receive oxcarbazepine only if the potential benefit justifies the potential risk.

Rare cases of anaphylaxis and angioedema involving the larynx, glottis, lips, and eyelids in patients after taking the first or subsequent doses of immediate-release (IR) oxcarbazepine have been reported. Angioedema associated with laryngeal edema can be fatal. If a patient develops any of these reactions after treatment with oxcarbazepine IR or ER, the drug should be discontinued and an alternative treatment started. These patients should not be rechallenged with the drug.

Clinically significant hyponatremia, defined as serum sodium level < 125 mmol/L, can develop during oxcarbazepine use and has generally occurred during the first 3 months of treatment. Some patients first developed hyponatremia > 1 year after initiation of therapy, which highlights the importance of monitoring serum sodium levels during maintenance treatment with oxcarbazepine. Monitoring should occur, particularly in patients receiving other medications known to decrease serum sodium levels, such as those associated with inappropriate antidiuretic hormone secretion or if symptoms develop that possibly indicate hyponatremia, such as lethargy, confusion, obtundation, or increase in seizure frequency or severity.

Serious dermatological reactions, including SJS and TEN, have been reported in both children and adults in association with oxcarbazepine use. The median time of onset for reported cases was 19 days. The presence of the HLA-B*1502 allele may put patients at an increased risk for SJS and TEN development. The risk of using oxcarbazepine in patients who carry the HLA-B*1502 allele should be carefully compared to the potential benefit.

There have been reports of DRESS, including fatal or life-threatening cases, with oxcarbazepine treatment. Early symptoms of hypersensitivity may be seen (fever, lymphadenopathy) even if a rash is not present. Oxcarbazepine should be stopped if alternative agents are appropriate for the patient.

CNS adverse events, classified as somnolence and fatigue, coordination difficulties, and behavioral abnormalities, have been reported in adult and pediatric patients treated with oxcarbazepine. Patients should be advised to not drive or operate machinery until there is sufficient experience to determine if central nervous system-related adverse reactions will impair these activities.

Exacerbation of or new onset of primary generalized seizures have been reported in patients on oxcarbazepine, particularly in pediatrics; if this occurs, oxcarbazepine should be discontinued.

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perampanel (Fycompa)

Perampanel carries a boxed warning for serious psychiatric and behavioral reactions. During phase 3 clinical trials, patients taking perampanel also exhibited an increased risk of hostile and aggressive behavior at a greater rate than patients receiving placebo. These effects were dose-related and typically emerged in the initial 6 weeks of therapy, although new events were seen to emerge through more than 37 weeks of therapy. Events included irritability, anger, aggression, and anxiety and were seen twice as often in the treatment group as compared to the placebo group. Additional issues including belligerence, affect liability, agitation, and physical assault were seen with some and reported as serious and/or life threatening. The events listed were seen in patients with and without a prior history of such behavior, psychiatric history, or use of other medications noted to cause hostility and aggression. Patients, caregivers, and family members should be instructed of the potential increased risk of psychiatric events with use of perampanel. Patients should be monitored for changes in behavior or mental status during treatment, particularly with higher doses and during titration. Monitoring should be continued for 1 month after the cessation of therapy. If any of the noted problems do occur, dosage should be reduced and subsequently discontinued if symptoms persist or worsen with patients being referred for a complete psychiatric evaluation.

The use of perampanel may increase the risk of suicidal thoughts or behavior in patients and the potential risk versus benefit should be considered. Patients receiving treatment with perampanel should be closely monitored for any signs of worsening depression, suicidal thoughts or behaviors, and/or changes in mood or behavior.

Perampanel may also cause certain neurologic effects including gait disturbances, dizziness, and somnolence. These effects generally occurred during the titration phase and were dose-dependent. Patients should be advised against engaging in potentially hazardous activities until the possible effects of perampanel use are determined.

In clinical trials, perampanel use showed an increased fall risk that resulted, in some cases, in head injuries along with bone fracture injuries. During phase 3 trials, 5% and 10% of patients randomized to perampanel 8 mg and 12 mg per day, respectively, reported falls compared to 3% for those receiving placebo. These falls, reported as serious, resulted in more frequent therapy discontinuation of perampanel compared to placebo. Elderly patients in the trials were at a greater risk of experiencing falls compared to younger adults and adolescents.

As with other antiepileptic drugs (AEDs), perampanel should be withdrawn slowly to minimize the potential for increased seizure activity, except in cases where the withdrawal is in response to severe adverse events.

The concomitant use of perampanel and CNS depressants, including alcohol, may increase CNS depressant effect.

phenytoin (Dilantin, Phenytek)

Phenytoin is contraindicated in those patients with a history of hypersensitivity to phenytoin or other hydantoins. It is not recommended in patients with a history of acute hepatotoxicity attributable to phenytoin. In addition, use of phenytoin in combination with delavirdine is contraindicated due to the potential for loss of virologic response and possible resistance to delavirdine and other non-nucleoside reverse transcriptase inhibitors.

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There have been a number of reports suggesting a relationship between phenytoin and the development of lymphadenopathy (local or generalized) including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's disease. Although a cause and effect relationship has not been established, the occurrence of lymphadenopathy indicates the need to differentiate such a condition from other types of lymph node pathology. Lymph node involvement may occur with or without symptoms and signs resembling serum sickness (e.g., fever, rash, liver involvement). In all cases of lymphadenopathy, follow-up observation for an extended period is indicated, and every effort should be made to achieve seizure control using alternative antiepileptic drugs.

Acute alcoholic intake may increase phenytoin serum levels, while chronic alcohol use may decrease serum levels.

Serious and sometimes fatal dermatologic reactions, including TEN and SJS, have been reported with phenytoin treatment. If a rash occurs, the patient should be evaluated for signs and symptoms of DRESS. The presence of HLA-B*1502, in patients of Chinese ancestry, may be a risk factor for the development of SJS/TEN.

There have been cases of bradycardia and cardiac arrest reported with the use of phenytoin at both therapeutic and toxic levels. Cardiac arrest occurred most often in patients with underlying cardiac disease.

primidone (Mysoline)

Primidone is contraindicated in patients with porphyria and patients who are hypersensitive to phenobarbital.

rufinamide (Banzel)

Rufinamide is associated with a decrease in the QT interval and is contraindicated in patients with familial short QT syndrome. Patients with this syndrome have an increased risk of sudden death and ventricular arrhythmias. Rufinamide should be used with caution in patients already receiving drugs that shorten the QT interval.

During clinical trials, patients younger than 12 years of age receiving rufinamide for at least 4 weeks experienced multi-organ hypersensitivity syndrome. The patients presented with a rash and at least 1 of the following symptoms: fever, elevated liver function tests, hematuria, and lymphadenopathy; however, due to the variability in the syndrome's expression, abnormalities in other organ systems may indicate the presence of this syndrome. If multi-organ hypersensitivity syndrome is suspected, rufinamide should be discontinued and an alternative therapy started. Also, patients who develop a rash without any other symptoms during treatment should be closely monitored.

To prevent the precipitation of seizures, seizure exacerbation, or status epilepticus during discontinuation, rufinamide should be gradually withdrawn by decreasing the dose by approximately 25% every 2 days. Patients who require abrupt discontinuation due to medical necessity should be closely monitored while being transitioned over to another agent.

topiramate (Qudexy XR, Topamax, Trokendi XR)

Hyperchloremic, non-anion gap, metabolic acidosis (e.g., decreased serum bicarbonate below the normal reference range in the absence of chronic respiratory alkalosis) is associated with topiramate

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treatment especially in children under 2 years of age with partial onset seizures. Metabolic acidosis is caused by renal bicarbonate loss due to the inhibitory effect of topiramate on carbonic anhydrase. Conditions or therapies that predispose to acidosis (such as renal disease, severe respiratory disorders, status epilepticus, diarrhea, surgery, ketogenic diet, or drugs) may add to the bicarbonate lowering effects of topiramate. Qudexy XR is contraindicated in patients with metabolic acidosis who are also taking concomitant metformin.

Oligohidrosis with topiramate, resulting in elevated body temperatures especially with exposure to elevated environmental temperatures, has resulted in hospitalization, especially in pediatric patients.

In pediatric and postmarketing clinical studies, topiramate has produced hyperammonemia (in some instances dose-related); reports occurred with and without encephalopathy. Symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy or vomiting. The hyperammonemia associated with topiramate treatment appears to be more common when topiramate is used concomitantly with valproic acid and may occur in patients who previously tolerated either drug alone. Hyperammonemia with and without encephalopathy has been observed in patients who were taking topiramate alone without concomitant valproic acid. Patients with inborn errors of metabolism or reduced hepatic mitochondrial activity may be at an increased risk.

During clinical trials in pediatric and adult patients, topiramate increased the risk for the formation of kidney stones. The incidence of stone formation in adults treated with immediate-release topiramate was 1.5%, or 2 to 4 times higher than a similar untreated population.

A syndrome consisting of acute myopia associated with secondary angle closure glaucoma has been reported in patients receiving topiramate. Symptoms include acute onset of decreased visual acuity and/or ocular pain. Ophthalmologic findings can include myopia, anterior chamber shallowing, ocular hyperemia (redness), and increased intraocular pressure. Mydriasis may or may not be present. This syndrome may be associated with supraciliary effusion resulting in anterior displacement of the lens and iris, with secondary angle closure glaucoma. Symptoms typically occur within 1 month of initiating topiramate. Visual field defects have been reported with topiramate independent of elevated intraocular pressure. If visual problems occur, consideration should be given to discontinuing the drug.

Topiramate can cause fetal harm when administered to a pregnant woman. Data from pregnancy registries indicate that infants exposed to topiramate in utero have an increased risk for cleft lip and/or cleft palate (oral clefts). When multiple species of pregnant animals received topiramate at clinically relevant doses, structural malformations, including craniofacial defects, and reduced fetal weights occurred in offspring.

Trokendi XR is contraindicated in patients who have consumed alcohol within 6 hours before and/or after the dose due to a significant alteration in topiramate release from the Trokendi XR capsules. In the presence of alcohol, topiramate plasma levels may be markedly higher soon after the dose and subtherapeutic the next day.

valproate/divalproex (Depakene, Depakote/ER)

Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid and its derivatives. Children under the age of 2 years are at increased risk of developing fatal hepatotoxicity, especially those on multiple anticonvulsants, those with congenital metabolic disorders, those with severe

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seizure disorders accompanied by mental retardation, and those with organic brain disease. When valproic acid/divalproex is used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. These incidents usually have occurred during the first 6 months of treatment. Serious or fatal hepatotoxicity may be preceded by nonspecific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and vomiting. In patients with epilepsy, a loss of seizure control may also occur. Patients should be monitored closely for appearance of these symptoms. Liver function tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first 6 months.

Valproate derivatives can produce teratogenic effects, such as neural tube defects and other structural abnormalities (e.g., craniofacial defects, cardiovascular malformations, hypospadias, limb malformations). Accordingly, the use of valproic acid/divalproex in women of childbearing potential requires that the benefits of its use be weighed against the risk of injury to the fetus.

Cases of life-threatening pancreatitis have been reported in both children and adults receiving valproate and its derivatives. Some of the cases have been described as hemorrhagic with a rapid progression from initial symptoms to death. Cases have been reported shortly after initial use, as well as after several years of use. Patients and caregivers should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt medical evaluation. If pancreatitis is diagnosed, valproate should be discontinued.

Valproate is associated with dose-related thrombocytopenia, as well as decreases in other cell lines and myelodysplasia. The benefit of high dose valproate should be weighed against the risk of a greater incidence of adverse reactions. DRESS has been reported in patients taking valproate.

Valproate/divalproex products are contraindicated in patients with hepatic disease or significant hepatic dysfunction, known hypersensitivity to the drug, urea cycle disorders, or for use as migraine prophylaxis in pregnant women.

Valproate/divalproex products are also contraindicated in patients with mitochondrial disorders caused by mutations in mitochondrial DNA polymerase γ (POLG; e.g., Alpers-Huttenlocher Syndrome) and children under 2 years of age who are suspected of having a POLG-related disorder.

vigabatrin (Sabril)

Vigabatrin can cause irreversible vision loss. Because of this, if clinical improvement is not seen within 2 to 4 weeks of treatment, vigabatrin should be discontinued. Vision testing should be administered at baseline, at least every 3 months while on therapy, and about 3 to 6 months after discontinuation.

Due to the irreversible vision loss, vigabatrin is available only through a special restricted distribution program under its REMS Program.[204] Under the REMS Program, only prescribers and pharmacies registered with the program are able to prescribe and distribute vigabatrin. Medication may only be dispensed to patients with documentation that they are informed of the risk of vision loss and need for frequent monitoring.

Patients may be exempted from vision assessment under limited conditions, including patient blindness or when the patient's general neurological and/or mental condition permanently precludes the need for visual assessment. Abnormal magnetic resonance imaging (MRI) signal changes and have also been reported with vigabatrin use.

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zonisamide (Zonegran)

Zonisamide is contraindicated in patients with hypersensitivity to sulfonamides. Zonisamide may cause a severe rash, including SJS and TEN. Patients who develop a rash should stop taking zonisamide. Hepatic necrosis, agranulocytosis, and aplastic anemia have also resulted from hypersensitivity. Oligohidrosis, hyperthermia, metabolic acidosis, and heat stroke have also been reported in patients on zonisamide. Pediatric patients appear to be at a greater risk.

Medication Guide/Risk Mitigation Evaluation Strategy (REMS)

The following products must be dispensed with a Medication Guide: brivaracetam (Briviact), cannabidiol (Epidiolex), carbamazepine (Equetro), clonazepam (Klonopin), ethotoin (Peganone), ethosuximide (Zarontin), gabapentin (Neurontin), lacosamide (Vimpat), lamotrigine (Lamictal, Lamictal ODT, Lamictal XR), levetiracetam (Keppra, Keppra XR, Spritam), methsuximide (Celontin), oxcarbazepine (Trileptal, Oxtellar XR), pregabalin (Lyrica), rufinamide (Banzel), tiagabine (Gabitril), topiramate (Qudexy XR, Topamax, Trokendi XR), and zonisamide (Zonegran).

In addition to a Medication Guide, vigabatrin (Sabril) is associated with a Communication Plan that will send Dear Healthcare Professional Letters to all registered ophthalmologists annually. The manufacturer must ensure proper training of all parties involved with the proper dispensing of vigabatrin. Elements to assure safe use mandate that healthcare providers and dispensing pharmacies issuing vigabatrin prescriptions be certified, and that vigabatrin is dispensed to recipients who meet treatment criteria. Vision assessments should be performed at initiation, every 3 months during therapy, and about 3 to 6 months after discontinuation; however, ophthalmologic assessment forms are no longer required as part of the REMS program.

DRUG INTERACTIONS[205,206,207,208,209,210,211,212,213,214,215,216,217,218,219,220,221,222,223,224,225,226,227,228,229,230,231,232,233,234,235,236,237,238,239,240,241,242,243,244,245]

There are many different drug interactions associated with each anticonvulsant agent. Phenobarbital, phenytoin (Dilantin, Phenytek), primidone (Mysoline), and carbamazepine (Tegretol, Tegretol XR, Carbatrol, Equetro, Epitol) are potent inducers of CYP 450 and other enzyme systems.

Barbiturates can induce hepatic microsomal enzymes resulting in increased metabolism and decreased anticoagulant response in oral anticoagulants (e.g., warfarin). Phenobarbital has been shown to shorten the half-life of doxycycline for as long as 2 weeks after barbiturate therapy is discontinued. MAO inhibitors prolong the effects of barbiturates probably because metabolism of the barbiturate is inhibited.

Ethosuximide (Zarontin) is metabolized mainly by CYP3A4 enzyme via hydroxylation to inactive metabolites. Drugs that inhibit, induce, or are metabolized by this enzyme can change the therapeutic levels of the active drug. Depending on the type of drug interaction, dosages of ethosuximide or the interacting drug may need to be adjusted and monitored. Ethosuximide does not inhibit or induce CYP 450 isozymes. Lacosamide (Vimpat) is a CYP2C9, CYP2C19, and CYP3A4 substrate, but it does not induce or inhibit CYP enzymes. Vigabatrin (Sabril) may induce CYP2C9 enzymes in some patients. Methsuximide may increase the plasma concentrations of phenytoin and phenobarbital.

Monitoring of plasma levels of the active metabolite of oxcarbazepine (Trileptal) should be considered when administered in conjunction with strong CYP3A4 or UGT inducers.

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The CNS-depressant action of the benzodiazepine class of drugs may be potentiated by alcohol, narcotics, barbiturates, nonbarbiturate hypnotics, anti-anxiety agents, phenothiazines, thioxanthene and butyrophenone classes of antipsychotic agents, MAO inhibitors, tricyclic antidepressants, and by other anticonvulsant drugs. There is no data to evaluate the interaction of rectally administered diazepam with other drugs; however, the potential for interaction by a variety of mechanisms exists.

Co-administration of carbamazepine and nefazodone may result in insufficient plasma concentrations of nefazodone and its active metabolite to achieve therapeutic effect. Co-administration of carbamazepine with nefazodone is contraindicated. Concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects. Concomitant use of carbamazepine and isoniazid has been reported to increase isoniazid-induced hepatotoxicity. Concomitant therapy with carbamazepine and some diuretics (hydrochlorothiazide, furosemide) may lead to symptomatic hyponatremia. Carbamazepine may antagonize the effects of nondepolarizing muscle relaxants (e.g., pancuronium). Alterations of thyroid function have been reported in combination therapy with other anticonvulsant medications. Co-administration of carbamazepine with direct-acting oral anticoagulants (e.g., apixaban, dabigatran, edoxaban, and rivaroxaban) may result in reduced plasma concentration of the anticoagulant decreasing the therapeutic effect. This combination should be avoided.

Eslicarbazepine acetate (Aptiom) can inhibit CYP2C19 and can elevate concentrations of phenytoin or other drugs metabolized by CYP2C19. *In vivo* studies suggest that it can induce CYP3A4, decreasing plasma concentrations of drugs that are metabolized by this isoenzyme (e.g., simvastatin), and several antiepileptics (e.g., carbamazepine, phenobarbital, phenytoin, primidone) can induce enzymes that metabolize eslicarbazepine acetate and can cause decreased plasma concentrations. Perampanel (Fycompa) is both a substrate and weak inducer of CYP3A4/5. Perampanel concentrations may be decreased by up to 50% to 67% when used concomitantly with cytochrome P450 (CYP) enzyme inducers, including phenytoin, oxcarbazepine, or carbamazepine, and starting doses should be increased when used with such inducers.

Rufinamide (Banzel) is a weak inducer of the CYP3A4 enzyme and has been shown to cause a decrease concentration of drugs that are substrates of the CYP3A4 enzyme. It is also a weak inhibitor of CYP2E1. Drugs that induce carboxylesterases, such as carbamazepine and phenobarbital, may decrease the concentration of rufinamide, while drugs that inhibit the carboxylesterase enzymes may increase the concentration of rufinamide. Rufinamide has been shown to increase the plasma concentration of phenytoin by ≥ 21% and valproic acid (Depakene) has been shown to increase the concentration of rufinamide up to 70%.

The concomitant use of topiramate (Qudexy XR, Topamax, Trokendi XR) with any other drug producing metabolic acidosis (e.g., zonisamide, acetazolamide, dichlorphenamide), or potentially in patients on a ketogenic diet, may create a physiological environment that increases the risk of kidney stone formation, and should therefore be avoided. Kidney stones have also been reported in pediatric patients prescribed topiramate for migraine prophylaxis. Concurrent use of metformin and topiramate is contraindicated in metabolic acidosis conditions.

Use of topiramate (Qudexy XR, Topamax, Trokendi XR) and valproic acid concurrently can result in hypothermia with or without hyperammonemia. Hypothermia is defined as a drop in core body temperature < 35°C (95°F). Hypothermia can present with a variety of symptoms that include lethargy, confusion, coma, and shifts in other major organ systems, including cardiovascular and respiratory systems. Clinical management should include stopping 1 of the medications and evaluation of

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ammonia levels. Dose-related hyperammonemia, with or without encephalopathy, has been reported with topiramate, particularly when used concomitantly with valproic acid.

A dosage adjustment of topiramate may be needed if used concomitantly with phenytoin or carbamazepine due to a significant decrease in plasma concentrations of topiramate.

Zonisamide (Zonegran) is principally inactivated by CYP3A4-dependent reduction; therefore, when used in combination with CYP3A4 inducers, its clearance is increased resulting in the possible necessity of a dosage increase.[246] Valproate derivatives (Depakene, Depakote/ER) inhibit many hepatic enzyme systems and can displace drugs from albumin.

Carbamazepine (40% to 90%), phenytoin (90%), primidone (80%), tiagabine (Gabitril) (95%), and valproic acid (80% to 95%) are highly bound to protein. Tiagabine is displaced from protein by naproxen, salicylates, and valproic acid. Valproic acid displaces diazepam, phenytoin, tolbutamide, and warfarin.

Brivaracetam (Briviact) may increase the active metabolite of carbamazepine (carbamazepine-epoxide); consider a dose reduction in patients if tolerability concerns arise. Brivaracetam dose should be increased by 100% in patients concurrently using rifampin due to CYP2C19 induction by rifampin.

There is concern related to increased risk of failure of oral contraceptives with use of cytochrome P450 3A4 enzyme-inducing AEDs, such as phenobarbital, carbamazepine, phenytoin, felbamate (Felbatol), topiramate (Qudexy XR, Topamax, Trokendi XR), oxcarbazepine (Trileptal, Oxtellar XR), eslicarbazepine acetate (Aptiom), clobazam (Onfi, Sympazan), perampanel (Fycompa), and rufinamide (Banzel). Since a particular antiepileptic drug may induce metabolism of the estrogen or the progestin and it is unclear which component is clinically more important in pregnancy prevention, it is recommended that women taking enzyme-inducing antiepileptic drugs should receive an oral contraceptive containing at least 50 mcg of ethinyl estradiol and that low-dose formulations should generally be avoided. Patients taking an oral contraceptive and rufinamide are recommended to use a secondary non-hormonal form of contraception. Antiepileptic drugs that do not induce cytochrome P450 3A4 enzymes, including gabapentin (Neurontin), levetiracetam (Keppra, Keppra XR, Spritam), tiagabine, zonisamide, vigabatrin, and pregabalin (Lyrica), do not interact with oral contraceptives. Lamotrigine (Lamictal, Lamictal XR) levels are reduced by 50% with use of oral contraceptives. Therefore, dose adjustment of lamotrigine may be required when oral contraceptives are initiated or discontinued, and it should be noted that clinical toxicity could occur during the placebo or pill-free week of the oral contraceptive regimen.[247] The use of concomitant antiepileptic drugs and other medications (e.g., rifampin, protease inhibitors) that induce the glucuronidation of lamotrigine must be considered when determining dosing regimens for lamotrigine in women already taking or initiating estrogen-containing oral contraceptives. Estrogen-containing contraceptives may increase the clearance of valproic acid and may lead to decreased valproic acid levels and increased incidence of seizures; valproic acid levels and clinical response should be monitored when adding or discontinuing estrogen-containing products.

Cannabidiol (Epidiolex) may cause clinically significant drug interactions with CYP2C8 and CYP2C9 (e.g., phenytoin) substrates. Additional monitoring for adverse events or decreased efficacy is recommended when cannabidiol is co-administered with substrates of UGT1A9, UGT2B7, CYP1A2, and CYP2B6. Dose reductions for 2C19 substrates may be required (e.g., diazepam, clobazam) if administered with cannabidiol. Clobazam and other CNS depressant medications may potentiate the somnolence effects of cannabidiol. Concomitant valproate increases the risk of hepatocellular injury and elevated liver

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transaminases requiring ongoing monitoring and possible dose adjustments for valproate and/or cannabidiol.

Medications metabolized through CYP2D6 may need to be adjusted when administered with clobazam (Onfi, Sympazan). Additionally, dosage adjustments of clobazam should occur when administered with strong inhibitors of CYP2C19 (e.g., fluconazole, fluvoxamine, ticlopidine), or moderate inhibitors (e.g., omeprazole). Administration with alcohol increases the maximum plasma exposure of clobazam by 50%.

Phenytoin is metabolized by CYP2C9 and CYP2C19, and is particularly susceptible to inhibitory drug interactions because it is subject to saturable metabolism. Inhibitory interactions may produce significant increases in circulating phenytoin concentrations and drug toxicity. Phenytoin is also a potent inducer of hepatic drug-metabolizing enzymes and administration may affect exposures to other drugs. Phenytoin also is extensively bound to serum plasma proteins and is subject to displacement.

Drugs that may increase phenytoin serum levels include: acute alcohol intake, various anti-epileptic agents, azoles, and a number of other agents. Drugs that may decrease phenytoin levels include: anti-cancer drugs, carbamazepine, chronic alcohol abuse, vigabatrin, and other agents. Preparations that increase gastric pH may affect phenytoin absorption, and usually results in a decrease in phenytoin bioavailability.

Phenobarbital, sodium valproate, and valproic acid may either increase or decrease phenytoin concentrations. Similarly, the effect of phenytoin on these agents is unpredictable.

The efficacy of azoles, corticosteroids, estrogens, and oral contraceptives, as well as a number of other drugs including paclitaxel, paroxetine, quinidine, rifampin, sertraline, teniposide, and theophylline, may be impaired by phenytoin.

In addition to concerns regarding underlying cardiac conduction abnormalities in patients using lacosamide (Vimpat), caution should be exercised for patients using medications that affect cardiac conduction. ECG monitoring is recommended at baseline and at steady-state for patients receiving lacosamide in addition to cardiac medications, such as sodium channel blockers, beta-blockers, calcium channel blockers, and potassium channel blockers.

Increased and decreased PT/INR responses have also been reported when phenytoin is co-administered with warfarin. Postmarketing experience with topiramate and vitamin K antagonist anticoagulants result in a decrease in PT/INR. In addition, administration of enteral feedings and nutritional supplements may decrease phenytoin levels.

Due to the high incidence of seizures, neurologic disorders, such as peripheral neuropathies, and psychiatric conditions, it is estimated that as many as 55% of HIV/AIDS patients may receive both anticonvulsant medications and antiviral therapy.[248] Thus, anticonvulsants that induce CYP450 enzymes, such as phenobarbital, carbamazepine, and phenytoin, may be expected to decrease exposures to non-nucleotide reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs), which could result in therapeutic failure. Alternatively, in some cases, anticonvulsants may reduce the clearance of antiviral agents and induce toxicities. Consequently, it may be important to avoid enzyme-inducing anticonvulsants in people on antiretroviral regimens that include PIs or NNRTIs. If such regimens are required for seizure control, pharmacokinetic monitoring may be necessary to ensure efficacy of the antiretroviral regimen.

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Drug Interactions Table

Drug	Substrate	Inhibitor	Inducer
barbiturates	--	--	CYP 1A2, 2B6, 2C8, 2C9, 2C18, 2C19, 3A4, 3A5-7
hydantoins	CYP 2C9, 2C19	--	CYP 1A2, 2B6, 2C8, 2C9, 2C18, 2C19, 3A4, 3A5-7
succinimides	CYP 3A4	--	CYP 3A4 (methsuximide only)
benzodiazepines	CYP 3A4 (clonazepam, clobazam) CYP 2B6, 2C19 (clobazam, diazepam) CYP 2C8, 2C9, 3A4, 3A5-7 (diazepam)	CYP 2C19, 3A4 (diazepam) CYP2D6 (clobazam)	CYP 3A4 (clobazam)
Carbamazepine Derivatives			
carbamazepine (Tegretol, Tegretol XR, Carbatrol, Equetro, Epitol)	CYP 3A4	--	CYP 1A2, 3A4
eslicarbazepine acetate (Aptiom)	--	CYP 2C19	CYP 3A4, UDPGT 1A1
oxcarbazepine (Trileptal, Oxtellar XR)	--	CYP 2C19	CYP 3A4, UGT
Valproic Acid Derivatives			
valproic acid, divalproex sodium, valproic acid ER (Depakene, Depakote, Depakote ER)	CYP 2C19	CYP 2C9, 2D6, 3A4	--
Other Anticonvulsants			
brivaracetam (Briviact)	CYP 2C19, 2C9	CYP 2C19	--
cannabidiol (Epidiolex)	CYP 2C19, 3A4 UGT 1A7, 1A9, 2B7	CYP 2C8, 2C9 UGT 1A9, 2B7	--
felbamate (Felbatol)	--	CYP 2C19	--
gabapentin (Neurontin)	Not metabolized		
lacosamide (Vimpat)	CYP 2C9, 2C19, 3A4	--	--
lamotrigine (Lamictal, Lamictal XR)	Greater than 75% metabolized in the liver by glucuronic acid conjugation; auto-induction may occur		
levetiracetam (Keppra, Keppra XR, Spritam)	Not extensively metabolized and not dependent on the CYP 450 isoenzymes		
perampanel (Fycompa)	CYP 3A4/5	--	CYP 3A4/5 UDPGT 1A1
pregabalin (Lyrica)	Not metabolized		
rufinamide (Banzel)	--	CYP 2E1	CYP 3A4
tiagabine (Gabitril)	CYP 3A4 possibly: 1A2, 2D6, 2C19	--	--
topiramate (Qudexy XR, Topamax, Trokendi XR)	CYP 2C19	CYP 2C19	CYP 3A4
vigabatrin (Sabril)	Not extensively metabolized, but may induce CYP 2C enzymes in some patients		
zonisamide (Zonegran)	CYP 3A4	--	--

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ADVERSE EFFECTS[249,250,251,252,253,254,255,256,257,258,259,260,261,262,263,264,265,266,267,268,269,270,271,272,273,274,275,276,277,278,279,280,281,282,283,284,285,286,287,288]

Drug	Nausea	Diarrhea	Weight Change	Tremor	Somnolence	Dizziness
Benzodiazepine Derivatives						
clobazam (Onfi, Sympazan)	nr	nr	nr	nr	22	reported
clonazepam (Klonopin)	reported	reported	reported	reported	7	< 1
diazepam rectal gel (Diastat)	nr	4	nr	nr	23	3
Carbamazepine Derivatives						
carbamazepine (Tegretol/XR, Carbatrol)	reported	reported	nr	nr	reported	reported
carbamazepine (Equetro)	29	10	nr	nr	32	44
eslicarbazepine acetate (Aptiom)	10-16 (5)	2-4 (3)	nr	2-4 (1)	11-18 (8)	20-28 (9)
oxcarbazepine (Oxtellar XR)	12	nr	nr	5 (1,200 mg/d) 1 (2,400 mg/d)	12 (1,200 mg/d) 14 (2,400 mg/d)	20 (1,200 mg/d) 41 (2,400 mg/d)
oxcarbazepine (Trileptal)	16	7	+ 2	4	28	22
Valproic Acid Derivatives						
valproic acid (Depakene), divalproex sodium (Depakote/ER)	34	23	+ 9	57	30	18
Other Anticonvulsants						
brivaracetam (Briviact)	5	nr	nr	nr	16	12
cannabidiol (Epidiolex)	nr	9-20 (9)	3-5 (1)	nr	23-25 (8)	nr
felbamate (Felbatol)	reported	5.2	- 3.4	reported	reported	reported
gabapentin (Neurontin)	reported	reported	+ 2.9	6.8	19.3	17.1
lacosamide (Vimpat)	7-17 (4)	3-5 (3)	nr	4-12 (4)	5-8 (5)	16-53 (8)
lamotrigine (Lamictal)	7	5	- 5	nr	nr	7
lamotrigine (Lamictal XR)	7 (8)	2 (5)	+ 2 (+ 1)	7 (2)	7 (2)	19 (5)
levetiracetam (Keppra, Spritam)	5	8	+ > 1	> 1	15	9
levetiracetam XR (Keppra XR)	5 (3)	nr	nr	nr	8 (3)	5 (3)
perampanel (Fycompa)	3-8 (5)	nr	+ 4 (1)	nr	9-18 (7)	16-43 (0)
pregabalin (Lyrica)	nr	nr	+ 4	8	7-20	10-39
rufinamide (Banzel)	7-12	nr	nr	6	11-17	8-19

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Adverse Effects (continued)

Drug	Nausea	Diarrhea	Weight Change	Tremor	Somnolence	Dizziness
Other Anticonvulsants *(continued)*						
tiagabine (Gabitril)	11	2-10	nr	9-21	18-21	27-31
topiramate (Qudexy XR, Topamax, Trokendi XR)	10-12	5-6	- 9-13	9	9-15	13-14
vigabatrin (Sabril)	2-10 (8)	10-16 (7)	+ 6 - +14 (+3)	15-16 (8)	22-26 (13)	24-26 (17)
zonisamide (Zonegran)	9	5	-3	nr	17	13

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported.

The adverse events for barbiturates, hydantoins, succinimides, and benzodiazepines are not quantified in the majority of the package inserts, but rather listed as occurring or not in a review of systems.

The most common adverse events that occurred in clinical trials of patients using brivaracetam not described above included fatigue (9%), cerebellar coordination/balance disturbances (3%), and irritability (3%).

Additional adverse reactions noted in clinical trials for cannabidiol and not described above include fatigue (11% to 12%), rash (7% to 13%), sleep disorder (5% to 11%), and infections (40% to 41%). Transaminase elevations (8% to 16%) were also reported for patients receiving cannabidiol. Baseline monitoring of serum transaminases and total bilirubin levels is recommended, in addition to reassessment at 1 month, 3 months, and 6 months following initiation of treatment. Repeat monitoring of liver function tests should be considered with dose adjustments, changes in concomitant medications, or the presentation of clinical signs or symptoms of hepatic dysfunction.

Carbamazepine (Tegretol, Tegretol XR, Carbatrol, and Equetro) may induce hyponatremia similar to the SIADH. Rashes are frequent, occurring in up to 9.9% of patients. Hematological adverse effects have also been reported. Agranulocytosis and aplastic anemia are rare. Thrombocytopenia and anemia have an incidence of less than 5% and usually respond to a cessation of therapy. Leukopenia is the most common hematological side effect with a 10% incidence. It is usually transient, persisting in about 2% of patients.[289]

Similar to carbamazepine, oxcarbazepine (Trileptal, Oxtellar XR) and eslicarbazepine acetate (Aptiom) are associated with hyponatremia (25% and 1.5%, respectively); this incidence does increase with age. Thirty percent of patients that have experienced a skin rash with carbamazepine will react similarly to oxcarbazepine.[290]

Common adverse reactions reported in clinical trials with clobazam that occurred at least 10% more frequently than placebo, include constipation, somnolence or sedation, pyrexia, lethargy, and drooling. Postmarketing reports have also cited urinary retention, hypothermia, diplopia, blurred vision, and various psychiatric disorders, such as agitation, anxiety, depression, and hallucination.

A drug reaction with eosinophilia and systemic symptoms was seen with ethosuximide (Zarontin).

Felbamate (Felbatol) is associated with a marked increase in the incidence of aplastic anemia (1 in 3,000 patients) and hepatitis (1 in 10,000 patients).[291] Accordingly, use only in patients whose epilepsy

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is so severe that the risk of aplastic anemia is deemed acceptable in light of the benefits conferred by its use.

Gabapentin (Neurontin) has an 8.3% incidence of nystagmus. This adverse effect has also been reported in clinical trials with oxcarbazepine (Trileptal; up to 2% with monotherapy; up to 26% with adjunctive therapy).

Diplopia may occur in 6% to 16% of patients taking lacosamide (Vimpat). Dose-dependent prolongations in PR interval may occur with lacosamide (Vimpat). First-degree AV block was observed in 0.4% of patients randomized to lacosamide and 0% with placebo. Second degree and complete AV block has also been reported and, when given with other drugs that prolong the PR interval, further PR prolongation is possible. Lacosamide may also predispose to atrial arrhythmias (atrial fibrillation or flutter), especially in patients with diabetic neuropathy and/or cardiovascular disease. Postmarketing reports have identified cardiac arrhythmias in patients treated with lacosamide, including bradycardia, AV block, and ventricular tachyarrhythmia. Asystole, cardiac arrest, and death have occurred with lacosamide in the oral and intravenous routes of administration and at various doses. Most cases occurred in patients who had an underlying proarrhythmic condition or were on a concomitant medication affecting cardiac conduction. A baseline ECG is recommended in addition to a repeat ECG when lacosamide has been titrated to a maintenance dose. DRESS has been reported with lacosamide treatment. This life-threatening multi-organ hypersensitivity reaction typically presents with fever, rash, lymphadenopathy, and facial swelling with other organ system involvement. If a provider suspects DRESS, lacosamide should be discontinued if an alternate cause cannot be identified.

Lamotrigine (Lamictal, Lamictal XR) therapy is associated with rashes; serious rashes requiring hospitalization and discontinuation of treatment have been reported in association with the use of lamotrigine. Pediatric patients on adjunctive therapy appear to have a higher risk of serious rash (8 in 1,000 patients) versus adult patients on adjunctive therapy (3 in 1,000 patients). Rashes are usually mild to moderate and associated with high initial doses, rapid titration, and concomitant valproate use (including valproic acid and divalproex sodium). SJS and TEN have also occurred with rare deaths reported. Although benign rashes also occur with lamotrigine, it is not possible to reliably predict which rashes will prove to be serious or life-threatening. Accordingly, lamotrigine should ordinarily be discontinued at the first sign of rash, unless the rash is clearly not drug-related.

Levetiracetam (Keppra, Spritam) is associated with a slight decrease in red and white blood cells, but levetiracetam XR (Keppra XR) has not demonstrated this in clinical studies; however, the manufacturer recommends monitoring the cell counts due to the results from the immediate-release formulation. Postmarketing reports have cited hyponatremia and acute kidney injury as an adverse reaction in patients taking levetiracetam (Keppra, Spritam) and levetiracetam XR (Keppra XR). Postmarketing reports have also shown that levetiracetam (Keppra, Spritam) is associated with muscle weakness and panic attack in patients.

SJS and TEN have also occurred with the use of immediate-release oxcarbazepine and therefore should be considered if a patient develops a skin reaction while taking oxcarbazepine extended-release (Oxtellar XR). In addition, patients carrying the Human Leukocyte Antigen (HLA) allele B*1502 may be at an increased risk for SJS or TEN with use of oxcarbazepine extended-release. Testing for the presence of the HLA-B*1502 allele should be considered in patients from certain populations with higher frequencies of the HLA-B*1502 allele (e.g., Han Chinese, Thai, Philippine, Malaysian populations).

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Cerebellar atrophy has been reported with phenytoin use, particularly in the settings of elevated phenytoin levels and/or long-term use.

There have been postmarketing reports of angioedema in patients during initial and chronic treatment with pregabalin (Lyrica). Specific symptoms included swelling of the face, mouth (e.g., tongue, lips, gums), and neck (e.g., throat, larynx). There were reports of life-threatening angioedema with respiratory compromise requiring emergency treatment. Pregabalin should be discontinued immediately in patients with these symptoms. Exercise caution when prescribing pregabalin to patients with a history of angioedema or who are already taking medications associated with angioedema such as angiotensin-converting enzyme (ACE) inhibitors.

Postmarketing reports have shown that tiagabine (Gabitril) is associated with seizures and status epilepticus in patients without epilepsy based on experience from off-label use. In most cases, patients were also taking medications known to lower the seizure threshold. Seizures and status epilepticus are known to occur with overdose. Also, tiagabine is associated with cognitive/neuropsychiatric adverse events, such as impaired concentration, speech or language problems, confusion, somnolence, and fatigue. These adverse events have led to 6% of patients receiving tiagabine versus 2% of patient receiving placebo to discontinue treatment during controlled clinical trials.

Topiramate (Qudexy XR, Topamax, Trokendi XR) is a carbonic anhydrase inhibitor. There is an increased rate of kidney stone formation (reduced urinary citrate excretion and increased urinary pH) with nephrolithiasis occurring in 1.5% of patients. Metabolic acidosis (due to renal loss of bicarbonate) may also develop because of carbonic anhydrase inhibition. Oligohidrosis, hyperthermia, and heat stroke have been reported, usually following exposure to elevated environmental temperatures. Finally, there are patients who have developed acute myopia and secondary angle-closure glaucoma. These symptoms seem to occur within the first month of therapy.

In placebo-controlled studies, bleeding was more frequently reported as an adverse event in patients taking topiramate (Topamax) than those taking placebo (4.5% versus 3%, respectively). Adverse reactions related to bleeding ranged from mild epistaxis and increased menstrual bleeding to hemorrhages. Patients with more serious bleeding events often had conditions that increased risk for bleeding or were taking drugs that may cause thrombocytopenia (e.g., other antiepileptic drugs) or affect platelet function (e.g., aspirin).

Thrombocytopenia is common in patients on valproic acid (Depakene) and divalproex (Depakote, Depakote ER).[292] It occurs in about 27% of patients and responds to a decrease in dose. Bone marrow changes also occur, as do leukopenia, transient neutropenia, and erythroblastopenia. There are at least 10 known metabolites; 1 may account for the reported fatal hepatotoxicities and is increased during dosing with enzyme-inducing drugs. This risk is higher in children and decreases in older age groups. Life-threatening pancreatitis has also been reported. Hyperammonemia may also occur, especially in patients with underlying urea cycle disorders. In addition, there have been postmarketing reports of encephalopathy without elevated ammonia levels. Parkinsonism has also been reported in postmarketing experience with valproic acid.

Zonisamide (Zonegran) is also a carbonic anhydrase inhibitor and a sulfonamide derivative. It is contraindicated in patients with sulfonamide allergy. Zonisamide causes hyperchloremic, non-anion gap, metabolic acidosis caused by renal bicarbonate loss resulting from its effect on carbonic anhydrase. Kidney stones are reported in approximately 4% of epilepsy patients on zonisamide.

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Pediatrics

Barbiturates are used for treatment of epilepsy in children. Dosage recommendations for primidone (Mysoline) exist for neonates, infants, and older children. There are dosage recommendations for phenobarbital for adolescents and older; dosage for infants and children should be individualized.

Dosage of the hydantoins in pediatric patients should be individualized and usually requires serum blood level determinations. Dosage of ethotoin (Peganone) in pediatric patients depends on the age and weight of the patient. Pediatric dosage of phenytoin (Dilantin, Phenytek) is based on weight; children > 6 years of age and adolescents may require the minimum adult dosage.

Ethosuximide (Zarontin) may be used in children 3 years of age and older. The initial dose for patients 3 to 6 years is 250 mg per day and for patients 6 years of age and older is 500 mg per day; thereafter, the dose should be individualized based on patient response and plasma level determinations. A smaller capsule providing a lower drug dosage of methsuximide (Celontin) is available for small children; optimal dosage must be determined by trial and should be kept at the lowest dose to control seizures so as to minimize adverse effects.

Specific dosage recommendations for clonazepam (Klonopin) exist for children 10 years of age and younger or who weigh < 30 kg. Recommended doses are meant to minimize drowsiness and provide seizure control. Clinical studies have not been conducted to establish the efficacy and safety of diazepam rectal gel (Diastat) or clobazam (Onfi, Sympazan) in children < 2 years of age.

Carbamazepine (Tegretol, Tegretol XR, Carbatrol, Epitol) can be used in pediatric patients with specific dosage recommendations for children < 6 years of age, children 6 to 12 years of age, and children older than 12 years of age. Dosage is ultimately determined by monitoring of blood levels and optimal clinical response. The therapeutic range is the same for both children and adults (4 to 12 mcg/mL). Carbamazepine ER (Equetro) has not been proven to be safe or effective in children or adolescents.

Cannabidiol (Epidiolex) is indicated for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients ≥ 2 years of age.

Eslicarbazepine acetate (Aptiom) is indicated for the treatment of partial-onset seizures in patients 4 years of age and older.

The safety and effectiveness of brivaracetam (Briviact) are established as monotherapy and adjunctive therapy for partial-onset seizures is approved in patients ≥ 4 years old.

Felbamate (Felbatol) is indicated in children only as adjunctive therapy for treatment of Lennox-Gastaut syndrome in patients 2 to 14 years of age and older.

Gabapentin (Neurontin) is indicated for treatment of partial seizures in children ≥ 12 years of age with epilepsy and as adjunctive therapy for treatment of partial seizures in children 3 to 12 years of age with epilepsy.

Oral formulations of lacosamide (Vimpat) are approved for the treatment of partial-onset seizures in patients ≥ 4 years of age. The safety of the injection in pediatric patients has not been established.

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Lamotrigine (Lamictal) is indicated for treatment of children ≥ 2 years of age for approved indications (partial seizures, the generalized seizures of Lennox-Gastaut syndrome, and primary generalized tonic-clonic [PGTC] seizures). Safety and effectiveness in patients < 18 years of age with bipolar disorder have not been established. Lamotrigine (Lamictal XR) is not approved for patients younger than 13 years of age.

Levetiracetam (Keppra, Spritam) is indicated as adjunctive therapy for treatment of myoclonic seizures in adolescents ≥ 12 years of age with juvenile myoclonic epilepsy. Levetiracetam (Keppra) is also used in the management of partial onset seizures in children 1 month of age and older with epilepsy, whereas levetiracetam (Spritam) is indicated for children 4 years of age and older (weighing > 20 kg) with epilepsy. Levetiracetam (Keppra, Spritam) is also indicated for the treatment of primary generalized tonic-clonic seizures in children 6 years of age and older with idiopathic generalized epilepsy. Levetiracetam extended-release (Keppra XR) is indicated as adjunctive therapy in the treatment of partial seizures in patients 12 years of age and older with epilepsy.

Oxcarbazepine (Trileptal) is indicated as monotherapy for treatment of partial seizures in children ≥ 4 years of age and as adjunctive therapy in children ≥ 2 years of age with partial seizures. Oxcarbazepine extended-release (Oxtellar XR) is indicated as adjunctive therapy of partial seizures in children ages 6 to 17 years. In children 4 to 12 years, weight-adjusted clearance is approximately 40% higher than adults. Oxcarbazepine ER has not been studied in children younger than 4 years of age, and is not approved for children < 6 years, due to the size of the tablet.

Perampanel (Fycompa) is indicated for the treatment of partial-onset seizures in patients ≥ 4 years of age. It is also indicated for adjunctive treatment for generalized tonic-clonic seizures in patients ≥ 12 years of age with epilepsy.

Pregabalin (Lyrica) is indicated as adjunctive therapy for the treatment of partial onset seizures in pediatric patients ≥ 4 years of age and older.

Tiagabine (Gabitril) is indicated as adjunctive therapy for treatment of partial seizures in children ≥ 12 years of age with epilepsy.

Rufinamide (Banzel) is indicated for adjunctive treatment for seizures associated with Lennox-Gastaut syndrome in patients ≥ 1 year of age. Studies indicate that the pharmacokinetics of rufinamide in pediatric patients and adolescents are similar to adults, but drug interactions tend to be more pronounced in pediatric patients.

Immediate-release topiramate (Topamax) and the extended-release formulation, Qudexy XR, are indicated as initial monotherapy for treatment of partial onset and primary generalized tonic-clonic seizures in children 2 years of age and older; however, the Trokendi XR extended-release formulation is only labeled for patients with this indication age ≥ 6 years. Immediate-release topiramate and Qudexy XR are also indicated as adjunctive therapy for treatment of partial onset and primary generalized tonic-clonic seizures in children 2 to 16 years of age and ≥ 2 years of age, respectively, and as adjunctive therapy in patients ≥ 2 years of age with seizures associated with Lennox-Gastaut syndrome. Trokendi XR is indicated as adjuvant therapy for the treatment of partial onset seizures, primary generalized tonic-clonic seizures, or Lennox-Gastaut syndrome in patients ≥ 6 years of age, whereas Qudexy XR is indicated for these indications in patients as young as 2 years of age. Pediatric patients have a 50% higher clearance of topiramate which results in a shorter elimination half-life than adults. Consequently, the plasma concentration for the same mg/kg dose may be lower in pediatric patients

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compared to adults. Topiramate (Qudexy XR, Topamax, Trokendi XR) is approved for migraine prophylaxis in children ≥ 12 years of age. In studies, the incidence of cognitive adverse reactions, such as difficulty with concentration and attention, was increased in pediatric patients treated with topiramate, as compared to placebo. Pediatric patients between the ages of 12 and 17 taking topiramate more frequently had elevated BUN, creatinine, uric acid, chloride, ammonia, total protein, and platelet levels.

Valproate has not been established to be safe and effective for the treatment of partial seizures in children < 10 years. Safety and efficacy of valproic acid for epilepsy and migraine prophylaxis has not been established in children less than 10 and 16 years of age, respectively.

Vigabatrin (Sabril) is approved for use in infants as young as 1 month to 2 years for treatment of infantile spasms, and for the adjunctive treatment of refractory complex partial seizures in children ≥ 10 years of age who have inadequately responded to several alternative treatments, if the benefits outweigh the risk of vision loss.

Although off-label use has been reported, safe and effective use of zonisamide (Zonegran) in children < 16 years of age has not been established. All patients, especially children, should be told to limit exposure to high ambient temperatures or other extremes that might aggravate temperature regulation. Concurrent use of medications that might predispose a patient to heat intolerance (anticholinergics) should be used cautiously with zonisamide (Zonegran).

Pregnancy

Freedom from seizures is the ultimate goal of treatment of patients with epilepsy; however, adverse effects of the antiepileptic drugs should not outweigh the benefits, particularly in women with epilepsy who wish to become pregnant. These women and their partners need to understand the risks associated with uncontrolled seizures, as well as the teratogenicity of some of the antiepileptic drugs.[333] Women who become pregnant while taking antiepileptic drugs should be encouraged to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. The registry is compiling safety information to assist with therapeutic decision making in this patient population.

Barbiturates and diazepam are classified as Pregnancy Category D. Labeling for carbamazepine (Carbatrol, Tegretol/XR), oxcarbazepine (Trileptal), phenytoin (Dilantin), ethotoin (Peganone), topiramate (Topamax), topiramate ER (Qudexy XR, Trokendi XR) was updated to comply with the Pregnancy and Lactation Labeling Rule (PLLR) and state that ingestion during pregnancy can cause fetal harm. Cannabidiol (Epidiolex), clonazepam (Klonopin), gabapentin (Neurontin), and clobazam (Onfi, Sympazan) labeling states that there are no adequate studies in pregnant women and the risk of teratogenicity is inconclusive. Some studies have indicated a higher risk of birth defects and possibly adverse cognitive effects with exposure to valproate compared to carbamazepine. Labeling for valproic acid (Depakene) and divalproex (Depakote, Depakote ER) was updated to comply with PLLR requirements. These agents contain a boxed warning regarding fetal risks, including neural tube defects, major malformations, neurodevelopmental disorders, and decreased intelligence quotient (IQ). These products should be avoided in women who are pregnant or plan to become pregnant when used for bipolar disorder or epilepsy unless other medications are not effective or cannot be tolerated. If used for migraine prophylaxis, these agents are contraindicated unless effective contraception is used.

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All of the drugs in this review of anticonvulsants, other than those named above, are classified as Pregnancy Category C.

Fetal hydantoin syndrome has been described in newborns exposed to phenytoin *in utero*. There is an increased frequency of orofacial clefts, cardiac defects, growth abnormalities, and cognitive deficits. The risk of orofacial defects in infants exposed to topiramate *in utero* is also increased based on data provided in pregnancy registries. Topiramate exposure may also lead to small size for gestational age.

A potentially life-threatening bleeding disorder related to decreased levels of vitamin K-dependent clotting factors may occur in newborns exposed to phenytoin *in utero*. This drug-induced condition can be prevented with vitamin K administration to the mother before delivery and to the neonate after birth.

Oxcarbazepine levels may decrease during pregnancy and patients should be monitored during pregnancy and through the postpartum period. While there are no well-controlled clinical studies of oxcarbazepine in pregnant women, it is structurally closely related to carbamazepine, which is considered to be teratogenic in humans. Pregnancy registry data on a small number of pregnancies show an association between oxcarbazepine and fetal congenital abnormalities such as craniofacial defects and cardiac malformations. It should be used during pregnancy only if the potential benefit justifies the potential risk.

Physiological changes associated in pregnancy, particularly the third trimester, may decrease plasma levels of levetiracetam. Close monitoring should continue during pregnancy and the postpartum period.

Renal Impairment

Dosage of phenobarbital should be reduced in patients with impaired renal function.

No dosage adjustment of brivaracetam (Briviact) is required for patients with impaired renal function. Brivaracetam has not been studied in patients with end-stage renal disease (ESRD) undergoing hemodialysis; use is not recommended in these patients.

Ethosuximide and methsuximide should be administered with extreme caution to patients with known renal disease. Periodic urinalysis tests should be performed for patients on these drugs. Ethosuximide and methsuximide do not have guidelines available for dose adjustment in patients with renal dysfunction.

Metabolites of clonazepam and diazepam are excreted by the kidneys; therefore, caution should be exercised in treating patients with impaired renal function. Clobazam (Onfi, Sympazan) does not require dosage adjustment in those with mild to moderate renal impairment, but this medication has not been studied in severe impairment of ESRD.

Felbamate should be used with caution in patients with renal dysfunction.

Dosage adjustments are recommended for gabapentin in patients with compromised renal function. Gabapentin has not been studied in pediatric patients with renal insufficiency.

The maximum dose of lacosamide (Vimpat) in patients with severe renal impairment is 300 mg/day. Lacosamide is removed by hemodialysis and a bolus of 50% of the dose is recommended after each dialysis session. Patients with severe renal impairment who are taking strong inhibitors of CYP3A4 and

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CYP2C9 may have a significant increase in exposure to lacosamide and dose reduction may be necessary.

Lamotrigine has not been extensively evaluated in patients with severe renal function impairment; therefore, this medication should be used cautiously in these patients.

Dosing of levetiracetam must be individualized based on a patient's renal function.

In patients with impaired renal function (creatinine clearance [CrCl] < 30 mL/min), oxcarbazepine and oxcarbazepine ER (Oxtellar XR) therapy should be initiated at 50% of the usual starting dose and titrated slowly to achieve the desired clinical response. In dialysis patients with ESRD, immediate-release oxcarbazepine (Trileptal) is recommended instead of oxcarbazepine ER.

Eslicarbazepine (Aptiom) clearance is decreased in patients with impaired renal function. Dosage adjustment is necessary in patients with CrCl < 50 mL/min. In ESRD, repeated hemodialysis removed eslicarbazepine metabolites from the systemic circulation. Maximum dose of eslicarbazepine in patients with moderate to severe renal impairment is 600 mg once daily.

Dose adjustment of perampanel (Fycompa) is not required in mild renal impairment. In patients with moderate renal impairment, close monitoring and slower titration should be considered. Use in patients with severe renal impairment or patients undergoing hemodialysis is not recommended.

The starting dose of oxcarbazepine (Trileptal) should be reduced by half (300 mg/day) in patients with impaired renal function (CrCl < 30 mL/min).

Adverse reactions to pregabalin are dose-dependent, and it is eliminated primarily by renal excretion; therefore, dosage should be adjusted in adults based on renal function as determined by creatinine clearance. Pregabalin (Lyrica) has not been studied in pediatric patients with compromised renal function.

No dosage adjustment is necessary in patients taking rufinamide with impaired renal function (CrCl < 30 mL/min), but hemodialysis has reduced the rufinamide exposure by about 30%. Adjustment of the dose during dialysis may be considered.

In patients with impaired renal function, 50% of the topiramate dose is recommended. Renally-impaired patients will require a longer time to reach steady state at each dose.

Information about how to adjust the vigabatrin dose in pediatric patients with renal impairment is unavailable. In adults, dose adjustment is necessary in patients with mild, moderate, and severe renal impairment.

Since zonisamide is excreted by the kidneys, patients with renal disease should be treated with caution; titration may need to be slower and monitoring more frequent.

Hepatic Impairment

Dosage of phenobarbital should be reduced in patients with impaired hepatic function.

Liver function tests should be performed if clinical evidence of liver dysfunction exists during therapy with ethotoin (Peganone). Signs of liver damage are justification for discontinuation of therapy.

The liver is the primary site of phenytoin biotransformation; therefore, patients with impaired hepatic function may show early signs of toxicity. As with all patients, phenytoin serum level concentrations

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should be monitored for optimal clinical effect and safe use of the medication. Phenytoin is highly protein bound and the free fraction changes in the presence of low albumin levels. Consequently, free rather than total phenytoin concentration should be monitored in the presence of low albumin levels.

Ethosuximide and methsuximide should be administered with extreme caution to patients with impaired hepatic function. Periodic liver function tests should be performed for patients on these drugs.

Clonazepam undergoes hepatic metabolism; therefore, it should not be used to treat patients with impaired hepatic function. Similarly, initial dosing for clobazam (Onfi, Sympazan) should be decreased to 5 mg/day for those patients with mild to moderate hepatic insufficiency. Limited information for administration of clobazam is available for those with severe hepatic impairment, so dosing recommendations cannot be made.

Felbamate should not be prescribed for anyone with a history of hepatic dysfunction as it carries a boxed warning related to hepatic failure.

Mild to moderate hepatic impairment did not affect the pharmacokinetics of oxcarbazepine (Trileptal) in hepatically-impaired patients after a single 900 mg oral dose, and no dose adjustment is recommended in patients with mild to moderate impairment. The pharmacokinetics of oxcarbazepine and the active monohydroxy metabolite (MHD) have not been evaluated in patients with severe hepatic impairment. Caution should be exercised when dosing immediate-release oxcarbazepine in severely impaired patients, and oxcarbazepine ER (Oxtellar XR) is not recommended in patients with severe hepatic impairment.

Dose adjustments of eslicarbazepine acetate (Aptiom) are not required in patients with mild to moderate hepatic impairment. Use in patients with severe hepatic impairment has not been studied, and is not recommended. The maximum dose of lacosamide (Vimpat) in patients with mild to moderate hepatic impairment is 300 mg/day. Use is not recommended in severe hepatic impairment. Patients with hepatic impairment who are taking strong inhibitors of CYP3A4 and CYP2C9 may have a significant increase in exposure to lacosamide and dose reduction may be necessary.

A dosage reduction of brivaracetam (Briviact) is required for all stages of hepatic impairment in adults (Child-Pugh A, B, and C). The recommended initial dose is 25 mg twice daily; the maximum recommended dose is 75 mg twice daily. In pediatric patients with hepatic impairment, dosage reductions are also recommended. The initial dose for pediatric patients with hepatic impairment weighing 11 kg to < 50 kg is 0.5 mg/kg/twice daily with a maximum dose of 2 mg/kg twice daily. The maximum dose for patients weighing 20 kg to < 50 kg is 1.5 mg/kg twice daily.

Initial and maximum dose reduction with slower dose titration is recommended in patients treated with cannabidiol (Epidiolex) who have moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment. Patients with moderate hepatic impairment, the recommended starting dose is 1.25 mg/kg twice daily titrated to a maximum of 5 mg/kg twice daily. Cannabidiol should be initiated at 0.5 mg/kg twice daily and titrated to maximum dose of 2 mg/kg twice daily in in patients with severe hepatic impairment.

Initial, escalation, and maintenance doses of lamotrigine should be reduced by 25% in patients with moderate and severe hepatic function impairment without ascites and by 50% in patients with severe hepatic function impairment with ascites.

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Due to higher exposures and a longer half-life of perampanel (Fycompa), dosage adjustment is recommended in patients with mild and moderate hepatic impairment receiving perampanel. Maximum recommended daily dose is 6 mg and 4 mg once daily for patients with mild and moderate hepatic impairment, respectively. Use in patients with severe hepatic impairment is not recommended.

The effects of hepatic impairment on the pharmacokinetics of rufinamide have not been studied; therefore, use in patients with severe hepatic impairment is not recommended. Caution should be exercised in treating patients with mild to moderate hepatic impairment.

Patients with impaired hepatic function may require reduced initial and maintenance doses of tiagabine and/or longer dosing intervals.

Liver disease impairs the capacity to eliminate valproate. Liver impairment is also associated with decreased albumin concentrations and larger unbound fractions (2 to 2.6 fold increase) of valproate. Therefore, monitoring of total concentrations may be misleading because free concentrations may be significantly increased in patients with hepatic disease whereas total concentrations may appear to be normal. Liver function tests should be performed prior to therapy with valproate and at frequent intervals thereafter, especially during the first 6 months of therapy.

Since zonisamide is metabolized by the liver, patients with hepatic disease should be treated with caution. Titration may need to be slower and monitoring more frequent.

The clearance of topiramate may be decreased in patients with hepatic impairment; however, the mechanism is not well understood and no dose adjustments are required.

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Drug	Initial Dose	Maximum Daily Dose	Pediatric Dose	Availability
Barbiturates*				
primidone (Mysoline)	100 mg to 125 mg	2,000 mg/day (divided 3 times daily)	< 8 years: 10 to 25 mg/kg/day	50 mg, 250 mg tablets
phenobarbital	10-20 mg/kg (load), then 1-3 mg/kg/day	180-300 mg/day (1 to 2 times daily)	3 to 8 mg/kg/day[374]	20 mg/5 mL elixir 15 mg, 16.2 mg, 30 mg, 32.4 mg, 60 mg, 64.8 mg, 97.2 mg, 100 mg tablets
Hydantoins				
ethotoin (Peganone)	250 mg 4 times a day	3 grams daily in 4 to 6 divided doses	500 mg to 1,000 mg daily	250 mg tablets
phenytoin (Dilantin)	100 mg 3 times a day	600 mg/day (divided 3 to 4 times daily; convert to once daily with Kapseal®)	4 to 8 mg/kg/day	30 mg, 100 mg phenytoin sodium ER Kapseals* 50 mg phenytoin base chewable tablets* 125 mg/5 mL phenytoin base suspension*
phenytoin (Phenytek)	100 mg 3 times a day	600 mg/day (divided 3 to 4 times a day and then convert to once daily)	4 to 8 mg/kg/day	200 mg, 300 mg phenytoin sodium ER capsules*
Succinimides				
ethosuximide (Zarontin)	250 mg to 500 mg per day	1.5 gm/day or until control is achieved with minimal side effects (divided 2 times a day)	20 mg/kg/day	250 mg capsules 250 mg/5 mL solution
methsuximide (Celontin)	300 mg daily	1.2 gm/day or until control is achieved with minimal side effects (divided 2 to 4 times a day)	Dosing not specified in label	300 mg capsules
Benzodiazepines				
clobazam (Onfi, Sympazan)	≤ 30 kg: 5 mg/day > 30 kg: 10 mg/day Poor CYP2C19 metabolizers, elderly, hepatic impairment: 5mg/day	≤ 30 kg: 20 mg/day > 30 kg: 40 mg/day	≤ 30 kg: 20 mg/day > 30 kg: 40 mg/day	10 mg, 20 mg tablets (Onfi) 2.5 mg/mL suspension (Onfi) 5 mg, 10 mg, 20 mg oral film (Sympazan)
clonazepam (Klonopin)	0.5 mg 3 times a day	20 mg/day (divided 3 times a day)	0.1 to 0.2 mg/kg/day	0.5 mg, 1 mg, 2 mg tablets; 0.125 mg, 0.25 mg, 0.5 mg, 1 mg, 2 mg orally disintegrating tablets (wafers; generic only)

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Dosages (continued)

Drug	Initial Dose	Maximum Daily Dose	Pediatric Dose	Availability
Carbamazepine Derivatives				
diazepam rectal gel (Diastat)	0.2 mg/kg 1 time and may repeat in 4 to 12 hours if needed	1 episode every 5 days or 5 episodes every month	0.2 to 0.5 mg/kg	2.5 mg (twin pack) 10 mg, 20 mg AcuDial (twin pack)
carbamazepine (Tegretol/XR, Carbatrol)	Epilepsy: 400 mg/day (200 mg twice daily for both IR and ER; give suspension 100 mg 4 times daily) May increase dose weekly by adding up to 200 mg/day; use a twice daily regimen for ER tablets or 3 to 4 times daily for other formulations Trigeminal neuralgia: 200 mg/day (100 mg twice daily for both IR and XR; give Carbatrol 200 mg 1 time on first day; give suspension 50 mg 4 times daily)	Epilepsy: 1,600 mg/day (twice daily for XR/ER and 3 to 4 times a day for IR) Trigeminal neuralgia: 1,200 mg/day	< 6 years: initial - 10 to 20 mg/kg/day twice daily or 3 times daily as tablets or 4 times daily as suspension; may increase dose weekly up to 35 mg/kg/day 6-12 years: Initial - 100 mg twice daily IR or ER tablets or 2.5 mL 4 times daily for suspension; may increase dose weekly by adding up to 100 mg/day using twice daily regimen of ER tablets or 3 to 4 times daily of other formulations up to 1,000 mg/day	200 mg tablets 200 mg tablets (branded generic Epitol®) 100 mg chewable tablets (generic only) 100 mg/5 mL suspension 100 mg, 200 mg, 400 mg XR tablets 100 mg, 200 mg, 300 mg ER capsules
carbamazepine (Equetro)	Bipolar Disorder/Epilepsy: 400 mg/day (twice a day) Trigeminal neuralgia: 200 mg/day (once daily)	Bipolar Disorder/Epilepsy: 1,600 mg/day (twice a day) Trigeminal neuralgia: 1,200 mg/day	Epilepsy: Initial – 200 mg twice daily; may increase in weekly increments of 200 mg/day as equally divided, twice-daily doses until an optimal response is achieved Maximum dose: 12 to 15 years 500 mg twice daily 15 to 18 years 600 mg twice daily	100 mg, 200 mg, 300 mg ER capsules

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Dosages (continued)

Drug	Initial Dose	Maximum Daily Dose	Pediatric Dose	Availability
Carbamazepine Derivatives *(continued)*				
eslicarbazepine acetate (Aptiom)	400 mg once daily; after 1 week, increase to 800 mg once daily	1,600 mg once daily	> 4 years: Initial -200 to 400 mg/day depending on body weight; may increase in weekly increments Weight-dependent targets range 600 to 1,200 mg/day	200 mg, 400 mg, 600 mg, 800 mg tablets
oxcarbazepine ER (Oxtellar XR)	600 mg (once daily) on an empty stomach; may increase dose weekly by adding up to 600 mg/day (once daily)	2,400 mg/day (once daily) on an empty stomach	≥ 6 years: Initial - 8 to 10 mg/kg/day (once daily) on an empty stomach; may increase dose weekly by 8 to 10 mg/kg increments (once daily) on an empty stomach, up to 600 mg/day Weight-dependent targets range 900 to 1,800 mg/day (once daily)	150 mg, 300 mg, 600 mg ER tablets
oxcarbazepine (Trileptal)	300 mg twice a day	2,400 mg/day (twice a day)	Weight-dependent targets range 900 to 2,100 mg/day	150 mg, 300 mg, 600 mg tablets 300 mg/5 mL suspension
Valproic Acid and Derivatives				
divalproex (Depakote/ER)	Epilepsy: 10-15 mg/kg/day Migraine prophylaxis (ER): 500 mg once daily	Epilepsy: 60 mg/kg/day (delayed release dosed twice a day; ER dosed once daily) Migraine prophylaxis (ER): 1,000 mg once daily	Epilepsy: ≥ 10 years: 10 to 15 mg/kg/day	125 mg, 250 mg, 500 mg delayed-release tablets 125 mg Sprinkle capsules 250 mg, 500 mg ER tablets
valproic acid (Depakene)	10 to 15 mg/kg/day (doses > 250 mg/day should be given in divided doses)	60 mg/kg/day (doses > 250 mg/day should be given in divided doses)	10 to 15 mg/kg/day	250 mg capsules 250 mg/5 mL syrup

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Dosages (continued)

Drug	Initial Dose	Maximum Daily Dose	Pediatric Dose	Availability
Other Anticonvulsants				
brivaracetam (Briviact)	Patients ≥ 16 years: 50 mg twice daily (may be decreased to 25 mg twice daily or increased as needed)	100 mg twice daily	Monotherapy or adjunctive therapy for partial-onset seizures: ≥ 4 years weighing 11 to < 20 kg: 0.5 to 2.5 mg/kg twice daily; ≥ 4 years weighing 20 to < 50 kg: 0.5 to 2 mg/kg twice daily; ≥4 years weighing ≥ 50 kg: 25 mg to 100 mg twice daily	10 mg, 25 mg, 50 mg, 75 mg, 100 mg tablets 10 mg/mL oral solution
cannabidiol (Epidiolex)	2.5 mg/kg twice daily	10 mg/kg twice daily	≥ 2 years: same as in adults	100 mg/1 mL solution
felbamate (Felbatol)	Patients ≥ 14 years: 1,200 mg/day (divided 3 to 4 times a day)	3,600 mg/day (divided 3 to 4 times a day)	15 to 45 mg/kg/day (divided 3 to 4 times a day)	400 mg, 600 mg tablets 600 mg/5 mL suspension
gabapentin (Neurontin)	Epilepsy: 300 mg 3 times a day Postherpetic Neuralgia: 30mg once daily	Epilepsy: 3,600 mg/day (divided 3 times a day) Postherpetic Neuralgia: 1,800 mg/day (divided 3 times a day)	3 to 11 years: 10 to 50 mg/kg/day (divided 3 times a day)	100 mg, 300 mg, 400 mg capsules 600 mg, 800 mg tablets 250 mg/5 mL solution
lacosamide (Vimpat)	Monotherapy: 100 mg twice daily Adjunctive therapy: 50 mg twice daily Alternate: 200 mg single loading dose, followed 12 hours later by 100 mg twice daily	Monotherapy: 300 mg to 400 mg daily in 2 divided doses Adjunctive therapy: 200 mg to 300 mg daily	4 to 16 years 11 to < 30 kg: 1 to 6 mg twice daily 30 to < 50 kg: 1 to 4 mg/kg twice daily; ≥ 50 kg – 50 mg to 200 mg twice daily;	50 mg, 100 mg, 150 mg, 200 mg tablets 10 mg/mL solution

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Dosages (continued)

Drug	Initial Dose	Maximum Daily Dose	Pediatric Dose	Availability
Other Anticonvulsants *(continued)*				
lamotrigine (Lamictal)	Not in combination with glucuronidase inducing drugs (carbamazepine, phenytoin, phenobarbital, or primidone) or valproate: 25 mg/day With valproate: 25 mg every other day With glucuronidase inducers and not valproate: 50 mg/day	Bipolar Disorder: Not in combination with enzyme inducing drugs or valproate 200 mg/day With valproate: 100 mg/day With enzyme inducers and not valproate: 400 mg/day Epilepsy: With valproate alone: 200 mg/day With enzyme inducers: 500 mg/day	For 2-12 years not taking valproate or glucuronidase inducers: 4.5 to 7.5 mg/kg/day (maximum 300 mg/day in 2 divided doses) With valproate and no inducers 1 to 5 mg/kg/day (maximum 200 mg/day in 1 or 2 divided doses) With glucuronidase inducers and no valproate 5 to 15 mg/kg/day (maximum 400 mg/day in 2 divided doses)	25 mg, 100 mg, 150 mg, 200 mg tablets 25 mg, 100 mg, 150 mg, 200 mg tablets (branded generic Subvenite™) 5 mg, 25 mg chewable tablets 25 mg, 50 mg, 100 mg, 200 mg ODT
lamotrigine (Lamictal XR)	1 tablet daily (Daily dosage same as Lamictal immediate release tablets)	1 tablet daily (Daily dosage same as Lamictal immediate release tablets)	1 tablet daily (Daily dosage same as Lamictal immediate release tablets)	25 mg, 50 mg, 100 mg, 200 mg, 250 mg, 300 mg tablets

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Dosages (continued)

Drug	Initial Dose	Maximum Daily Dose	Pediatric Dose	Availability
Other Anticonvulsants *(continued)*				
levetiracetam (Keppra)	500 mg twice a day	1,500 mg twice a day	Adjunctive therapy for partial seizures: 1 month to < 6 months: initial – 7 mg/kg twice daily; recommended – 21 mg/kg twice daily 6 months to < 4 years: initial – 10 mg/kg twice daily; recommended – 25 mg/kg twice daily 4 to < 16 years: initial - 10 mg/kg twice daily; recommended – 30 mg/kg twice daily Adjunctive therapy for myoclonic seizures: ≥ 12 years: initial – 500 mg twice daily; recommended – 1,500 mg twice daily Adjunctive therapy for primary generalized tonic-clonic seizures: 6-16 years: initial – 10 mg/kg twice daily; recommended – 30 mg/kg twice daily	250 mg, 500 mg, 750 mg, 1,000 mg tablets 500 mg, 750 mg, 1,000 mg tablet (branded generic Roweepra™) 100 mg/mL solution
levetiracetam (Spritam)	500 mg twice a day May also be administered as an oral suspension by adding to a small amount of liquid and then swallowing	1,500 mg twice a day	Adjunctive therapy for partial seizures: ≥ 4 years weighing > 40 kg: same as in adults ≥ 4 years weighing 20 - 40 kg: initial – 250 mg twice daily; maximum – 750 mg twice daily Adjunctive therapy for myoclonic seizures: ≥ 12 years: same as in adults Adjunctive therapy for primary generalized tonic-clonic seizures: ≥ 6 years weighing > 40 kg: same as in adults ≥ 6 years weighing 20 - 40 kg: initial – 250 mg twice daily; maximum – 750 mg twice daily	250 mg, 500 mg, 750 mg, 1,000 mg orally disintegrating tablets

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Dosages (continued)

Drug	Initial Dose	Maximum Daily Dose	Pediatric Dose	Availability
Other Anticonvulsants *(continued)*				
levetiracetam XR (Keppra XR)	1,000 mg once daily	3,000 mg once daily	≥ 12 years: same as in adults	500 mg, 750 mg tablets 500 mg, 750 mg tablets (branded generic Roweepra XR™)
perampanel (Fycompa)	2 mg once daily at bedtime (4 mg once daily in patients on enzyme inducing AEDs)	12 mg once daily at bedtime	≥ 4 years: same as in adults	2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg tablets 0.5mg/mL oral suspension
pregabalin (Lyrica)	Adjunctive therapy for partial seizures: 150 mg/day in 2 to 3 divided doses	Adjunctive therapy for partial seizures: 600 mg/day	≥ 4 years weighing 11 to < 30 kg: 3.5 mg/kg/day in 2 to 3 divided doses; maximum 14 mg/kg/day in 2 to 3 divided doses ≥ 4 years weighing ≥ 30 kg: 2.5 mg/kg/day in 2 to 3 divided doses; maximum 10 mg/kg/day (not to exceed 600 mg/day) in 2 to 3 divided doses	25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, 300 mg capsules 20 mg/mL solution
rufinamide (Banzel)	400-800 mg/day in 2 equally divided doses with food	3,200 mg/day in 2 equally divided doses with food	1 year to < 17 years: 10 mg/kg/day in 2 equally divided doses; maximum 45 mg/kg/day or 3,200 mg in 2 equally divided doses with food	200 mg, 400 mg tablets 40 mg/mL suspension
tiagabine (Gabitril)	4 mg/day (with enzyme-inducing antiepileptic drugs)	56 mg/day (with enzyme-inducing antiepileptic drugs) (2 to 4 times a day)	12-18 years: up to 32 mg/day (with enzyme-inducing antiepileptic drugs)	2 mg, 4 mg, 12 mg, 16 mg tablets
topiramate (Topamax)	25-50 mg/day in 2 divided doses	400 mg/day in 2 divided doses	Monotherapy: 2-9 years: 25 mg/day nightly for first week and titrated based on tolerance and seizure control (maximum dose based on weight) > 10 years: same as in adults Adjunctive therapy: 2-16 years: 5-9 mg/kg/day in 2 divided doses Migraine Prophylaxis: ≥ 12 years 100 mg in 2 divided doses	25 mg, 50 mg, 100 mg, 200 mg tablets 15 mg, 25 mg Sprinkle capsules

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Dosages (continued)

Drug	Initial Dose	Maximum Daily Dose	Pediatric Dose	Availability
Other Anticonvulsants *(continued)*				
topiramate XR (Qudexy XR)	25-50 mg daily	400 mg daily	Monotherapy: 2-9 years: 25 mg/day nightly for the first week; titrate based on tolerance and seizure control (maximum dose based on weight) > 10 years: same as in adults Adjunctive therapy: 2-16 years: 5-9 mg/kg/day in 2 divided doses Migraine prophylaxis: ≥ 12 years: 100 mg once daily	25 mg, 50 mg, 100 mg, 150 mg, 200 mg ER capsules
topiramate XR (Trokendi XR)	25-50 mg daily	400 mg daily	Monotherapy: 6 to 9 years: 25mg/day nightly for the first week and titrated based on tolerance and seizure control (maximum dose based on weight) > 10 years: same as in adults Adjunctive therapy: 6-16 years: Approximately 5-9 mg/kg once daily; 25 mg/day nightly for the first week and titrated based on tolerance and seizure control (maximum dose based on weight) Migraine prophylaxis: ≥ 12 years: 100 mg once daily	25 mg, 50 mg, 100 mg, 200 mg ER capsules

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Dosages (continued)

Drug	Initial Dose	Maximum Daily Dose	Pediatric Dose	Availability
Other Anticonvulsants *(continued)*				
vigabatrin (Sabril)	500 mg twice daily	1,500 mg twice daily	10-16 years and 25-60 kg: 250 mg twice daily titrated to a maximum 1,000 mg twice daily 10-16 years and > 60 kg: same as in adults Infantile Spasms: 50 mg/kg/day in 2 divided doses, titrated to a maximum of 150 mg/kg/day	500 mg tablets 500 mg powder for oral solution
zonisamide (Zonegran)	100 mg daily	600 mg/day (1 to 2 times a day)	--	25 mg, 50 mg (generic only), 100 mg capsules

* Dilantin is available as 30 mg and 100 mg Extended-Release Kapseals expressed in terms of phenytoin sodium. Whereas the 50 mg chewable tablets and 125 mg/5 mL suspension are immediate-release formulations expressed in terms of phenytoin base. Interchange of the immediate-release and extended release formulations require not only accounting for differences in the frequency of administration but also that the ER formulations are 92% of the labeled dose in terms of phenytoin base as compared to 100% of the labeled dose as phenytoin base for the immediate-release formulations. Failure to adjust for this difference when switching formulations can result in toxicity or loss of efficacy due to the narrow therapeutic range and the nonlinear kinetics often observed with clinical dosages. Phenytek is also only available as extended-release capsules of phenytoin sodium expressed in terms of the salt. Dosage changes may need to be made for each agent based on the other anticonvulsants that the patient is currently receiving, decreased renal and/or hepatic function, and tolerability of the agent. Please consult package inserts for additional information.

carbamazepine: When converting patients from carbamazepine IR to Tegretol XR or Carbatrol, the same total daily dose should be administered. Tegretol XR tablets must be swallowed whole and never crushed or chewed.

lacosamide: Lacosamide may be initiated with a single loading dose of 200 mg under medical supervision due to increased incidence of CNS adverse reactions. The loading dose is to be followed 12 hours later by 100 mg twice daily; this regimen should be continued for 1 week.

levetiracetam: Levetiracetam (Spritam) is intended to disintegrate in the mouth with a sip of liquid before swallowing. A Spritam tablet may also be added to approximately 1 tablespoon of liquid in a cup and allowed to disperse prior to consumption of the entire contents. After administration of the suspension, any remaining residue should be re-suspending with an additional small volume of liquid and swallowed.

oxcarbazepine ER: In conversion of oxcarbazepine immediate-release to extended-release (Oxtellar XR), higher doses of Oxtellar XR may be needed, as the ER product is not bioequivalent to the same total dose of IR formulation.

phenytoin: Dilantin Kapseals and Phenytek are extended-release capsules formulated with the sodium salt of phenytoin. They are initiated 3 times daily, and then the patient is converted to once daily dosing when adequate seizure control is attained. The free acid form of phenytoin is used in the

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Dilantin-125 Suspension and Dilantin Infatab® formulations. There is an 8% increase in drug with the free acid products. They are not to be used for once daily dosing.

valproic acid and derivatives: There are several derivatives of valproic acid available. Each equivalent dosage form (Depakene versus Depakote) delivers the same amount of valproate ion. Depakote causes fewer gastrointestinal adverse effects than Depakene.

When converting patients from twice daily Depakote to once daily Depakote ER, an 8 to 20% higher total daily dose of Depakote ER should be given. They are not bioequivalent and dosage adjustments may be required.

In addition to its use in epilepsy, divalproex ER (Depakote ER) is indicated for use in acute manic or mixed episodes associated with bipolar disorder, with or without psychotic features. The initial dose is 25 mg/kg/day and can be increased to a maximum of 60 mg/kg/day to achieve therapeutic response. It is also indicated for migraine prophylaxis; the starting dose is 500 mg daily for 1 week, and then 1,000 mg daily.

Patients stabilized on rufinamide (Banzel) prior to being prescribed valproate should start valproate therapy at a low dose and titrate to a clinically effective dose.

vigabatrin: Vigabatrin is only available through pharmacies enrolled in the Vigabatrin REMS Program.

CLINICAL TRIALS

Search Strategy

Due to the multiple indications for use of the anticonvulsant medications, many of the comparative clinical trials currently available do not specifically focus on treatment of seizure disorder. However, the studies identified in this review attempt to isolate those comparative studies that facilitate identification of the clinically proven therapies in the treatment of seizure disorder that meet the goals of treatment for seizure disorder: reducing the frequency of seizures and providing the optimal quality of life for the patient. When comparative trial information was unavailable, well-designed placebo-controlled studies have been included.

Articles were identified through searches performed on PubMed and review of information sent by the manufacturers. The search strategy included the use of all drugs in this class and the keywords "seizure" and "anticonvulsants." Randomized, controlled, comparative trials of FDA-approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

The efficacy of clobazam oral film (Sympazan) is based upon bioavailability studies comparing it to the clobazam tablets (Onfi).[375]

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Seizure Disorders

brivaracetam (Briviact) versus placebo

The approval of brivaracetam as adjunctive therapy for partial-onset seizures was based on established effectiveness in three phase 3, fixed-dose, multicenter, randomized, double-blind, placebo-controlled clinical trials.[376,377,378,379] In Study 1, adults 16 to 70 years of age were randomized 1:1:1:1 to 20 mg, 50 mg, or 100 mg per day of brivaracetam or placebo (n=399). The primary endpoint, percent reduction in 7-day partial-onset seizure frequency over placebo in the modified intent-to-treat (mITT) population, was 6.8% (p=0.239), 6.5% (p=0.261), and 11.7% (p=0.037) for brivaracetam 20 mg, 50 mg, and 100 mg, respectively. In Study 2, adults 16 to 70 years of age were randomized to 1:1:1:1 to 5 mg, 20 mg, or 50 mg per day of brivaracetam or placebo (n=400). The primary endpoint, percent reduction in 7-day partial-onset seizure frequency over placebo in the mITT population, was -0.9% (p=0.885), 4.1% (p=0.492), and 12.8% (p=0.025) in the brivaracetam 5 mg, 20 mg, and 50 mg groups, respectively. In Study 3, adults 16 to 80 years of age were randomized 1:1:1 to 100 mg or 200 mg per day of brivaracetam or placebo (n=768). The primary endpoint, percent reduction in 28-day partial-onset seizure frequency over placebo in the mITT population, was 22.8% (95% confidence interval [CI], 13.3 to 31.2; p<0.001) for brivaracetam 100 mg/day and 23.2% (95% CI, 13.8 to 31.6; p<0.001) for brivaracetam 200 mg/day. Also, the 50% responder rates for brivaracetam 100 mg/day and 200 mg/day were 38.9% and 37.8%, respectively, versus 21.6% for placebo (p<0.001 for both comparisons versus placebo).

cannabidiol (Epidiolex) versus placebo

In a double-blind, placebo-controlled, 14-week trial, 225 patients with Lennox-Gastaut syndrome were randomized to 10 mg/kg of cannabidiol oral solution, 20 mg/kg cannabidiol oral solution, or placebo.[380] During the 28-day baseline period, patients who experienced ≥ 2 drop seizures despite treatment with conventional antiepileptic drugs were eligible for the study. The primary efficacy measure was the percentage change in the frequency of drop seizures from baseline to study completion. Compared to placebo, treatment with 20 mg/kg and 10 mg/kg of cannabidiol resulted in a 41.9% reduction (p=0.005) and 37.2% reduction (p=0.002) in drop seizures, respectively.

A double-blind, placebo-controlled trial of 120 patients aged 2 to 18 years of age with Dravet syndrome were randomized to receive cannabidiol solution (20 mg/kg/day) or placebo for 14 weeks.[381] During the 4 week baseline period, patients were required to have ≥ 4 convulsive seizures despite treatment with conventional antiepileptic drugs. The primary efficacy measure was the percentage change in the frequency of convulsive seizures from baseline to the completion of the 14-week treatment period. Patients treated with cannabidiol experienced a 39% decrease in convulsive seizures compared to a 13% reduction in the placebo group (p=0.01).

clobazam (Onfi) versus placebo

A randomized double-blind 12-week trial in 238 patients with poorly controlled Lennox-Gastaut Syndrome (LGS) compared adjunctive clobazam to placebo.[382,383] The study included a 4-week baseline period followed by a 3-week titration period and 12-week maintenance period. Patients were between the ages of 2 to 54 years with a current or prior diagnosis of LGS and stratified into 2 weight groups (12.5 kg to 30 kg versus > 30 kg). They were then randomized to placebo or 1 of 3 target maintenance doses: low, medium, or high dose. For the patients of smaller weight, the doses were 5 mg, 10 mg, or 20 mg daily. For the patients of higher weight, the doses were 10 mg, 20 mg, or 40 mg

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daily. The primary efficacy measure was the percent reduction in the weekly frequency of drop seizures (atonic, tonic, or myoclonic), also known as drop attacks, from the 4-week baseline period to 12-week maintenance period. The pre-dosing baseline average for weekly drop seizure frequency was 98, 100, 61, and 105 for the placebo, low-, medium-, and high-dose groups, respectively. There was a decrease of drop seizure frequency of 12.1%, 41.2%, 49.4%, and 68.3% for the placebo, low-, medium-, and high-dose groups, respectively ($p \leq 0.05$). The effects of clobazam appeared to be dose-dependent. There was no evidence that tolerance to the therapeutic effect of clobazam occurred during the 3-month maintenance period.

diazepam rectal gel (Diastat) versus placebo

In a double-blind, parallel-group, placebo-controlled study of home-based treatment for acute repetitive seizures patients were randomized to receive either rectal diazepam gel (n=64), at a dosage varying from 0.2 to 0.5 mg per kilogram of body weight on the basis of age, or placebo (n=61).[384] Children received 1 dose at the onset of acute repetitive seizures and a second dose 4 hours later. Adults received 3 doses – 1 dose at onset and 2 more doses 4 and 12 hours after onset. Treatment was administered by a caregiver who had received special training. The number of seizures after the first dose was counted beginning immediately after the first dose and continued for 12 hours in children and 24 hours in adults. Of 125 study patients with a history of acute repetitive seizures (ARS), 91 (47 children and 44 adults) were treated for an exacerbation of seizures during the study period. Diazepam treatment was superior to placebo with regard to the outcome variables related to efficacy: reduced seizure frequency ($p<0.001$) and improved global assessment of treatment outcome by the caregiver (frequency and severity of seizures and drug toxicity) ($p<0.001$). Post hoc analysis showed diazepam to be superior to placebo in reducing seizure frequency in both children ($p<0.001$) and adults ($p=0.02$), but only in children was it superior with regard to improvement in global outcome ($p<0.001$). The time to the first recurrence of seizures after initial treatment was longer for the patients receiving diazepam ($p<0.001$).

eslicarbazepine acetate (Aptiom) versus placebo

Eslicarbazepine acetate was compared to placebo as adjunctive therapy in adults with partial-onset seizures in 3 randomized, double-blind, placebo-controlled trials.[385] Enrolled subjects had partial-onset seizures with or without secondary generalization and were not adequately controlled with 1 to 3 concomitant AEDs. Two-thirds (69%) of subjects used 2 concomitant AEDs and 28% used 1 concomitant AED. The most commonly used AEDs were carbamazepine (50%), lamotrigine (24%), valproic acid (21%), and levetiracetam (18%). Oxcarbazepine was not allowed as a concomitant AED. Following an 8-week baseline phase that established baseline seizure frequency, subjects were randomized and then entered a treatment period consisting of an initial titration phase (2 weeks), and a subsequent maintenance phase (12 weeks). The titration schedule differed amongst the 3 studies. Thus, patients were started on a daily dose of 400 mg or 800 mg and subsequently increased by 400 mg/day following 1 or 2 weeks, until the final daily target dose of 800 mg or 1,200 mg was achieved. Studies 1 and 2 compared eslicarbazepine acetate doses of 400 mg, 800 mg, and 1,200 mg once daily with placebo, and study 3 compared dosages of 800 mg and 1,200 mg once daily with placebo. The mean standardized seizure frequency during the maintenance phase over 28 days was the primary efficacy endpoint in all 3 trials. Eslicarbazepine acetate 400 mg/day was studied in Studies 1 and 2 and did not show a significant treatment effect. At doses of 800 mg/day, mean seizure frequency was lower with eslicarbazepine acetate compared to placebo in Studies 1 (5 versus 6.6, $p=0.047$) and Study 2 (6.2

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versus 8.6, p=0.006), but not in Study 3 (6.5 versus 7.9, p=0.058). At 1,200 mg/day, all 3 studies demonstrated a lower seizure frequency with eslicarbazepine acetate as compared to placebo. Seizure frequencies with eslicarbazepine acetate 1,200 mg/day compared to placebo were (4.3 versus 6.6, p=0.001) in Study 1, (6.6 versus 8.6, p=0.042) in Study 2, and (6 versus 7.9, p=0.004) in Study 3.

ethosuximide (Zarontin) versus valproic acid (Depakene) versus lamotrigine (Lamictal)

In a double-blind, randomized, controlled clinical trial, the efficacy, tolerability, and neuropsychological effects of ethosuximide, valproic acid, and lamotrigine in children with newly-diagnosed childhood absence epilepsy (n=453) were compared.[386] Drug doses were increased until the child was free of seizures, the maximal allowable or highest tolerable dose was reached, or a criterion indicating treatment failure was met. The primary outcome was freedom from treatment failure after 16 weeks of therapy. Differential drug effects were determined by means of pairwise comparisons. After 16 weeks of therapy, the freedom-from-failure rates for ethosuximide and valproic acid were similar (53% and 58%, respectively; p=0.35) and were higher than the rate for lamotrigine (29%; p<0.001 for both comparisons). There were no significant differences among the 3 drugs with regard to discontinuation because of adverse events. Lamotrigine is not indicated for the treatment of absence seizures.

gabapentin (Neurontin) versus carbamazepine (Tegretol)

Gabapentin and carbamazepine have been compared in a randomized, double-blind manner for the treatment of partial or generalized epilepsy in 292 patients.[387] They were similar in efficacy with more carbamazepine patients discontinuing therapy due to adverse effects than gabapentin patients (24% versus 13.5%).

gabapentin (Neurontin) or lamotrigine (Lamictal) versus carbamazepine (Tegretol)

An 18-center, randomized, double-blind, double-dummy, parallel study of 593 elderly patients with newly diagnosed seizure disorder was conducted to determine the relative tolerability and efficacy of 2 anticonvulsants, lamotrigine and gabapentin, as compared to carbamazepine.[388] Patients (mean age 72 years) were randomly assigned to 1 of 3 treatment groups: gabapentin 1,500 mg daily, lamotrigine 150 mg daily, and carbamazepine 600 mg daily. The primary outcome measure was retention in the trial for at least 12 months. Most patients had multiple medical conditions, received an average of 7 concomitant medications, and had a history of cerebral infarction. There was no significant difference in seizure-free rate at 12 months. However, the incidence of adverse effects that resulted in termination of therapy was 12.1% for lamotrigine, 21.6% for gabapentin, and 31% for carbamazepine (p=0.001). The study concluded that lamotrigine and gabapentin should be considered as initial therapy for older patients with newly diagnosed seizures.

lacosamide versus controlled-release carbamazepine

A phase 3, double-blind, non-inferiority trial randomized 888 patients 16 years of age or older with newly diagnosed epilepsy 1:1 to lacosamide monotherapy or carbamazepine CR twice daily.[389] During the first 2 weeks, doses were titrated to the first target level of lacosamide 200 mg/day and carbamazepine CR 400 mg/day. After a 1-week stabilization period, patients entered a 6-month assessment period. If a seizure occurred, the dose was titrated to the next target level (lacosamide 400 mg or 600 mg/day and carbamazepine CR 800 mg or 1,200 mg/day) over 2 weeks with a 1-week stabilization period, and then another 6-month assessment. Patients who completed 6 months of treatment and remained seizure-free entered a 6-month maintenance period with the existing dose.

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The primary efficacy outcome of proportion of patients remaining free from seizures for 6 consecutive months after stabilization at the last assessed dose was achieved by 74% of patients on lacosamide and 70% on carbamazepine CR. Treatment-related adverse events were reported in 74% patients treated with lacosamide and 75% treated with carbamazepine CR. Lacosamide met the predefined criteria for non-inferiority (-12% absolute and -20% relative difference between treatment groups).

lamotrigine (Lamictal) versus carbamazepine (Tegretol) or phenytoin (Dilantin)

Lamotrigine has been compared to carbamazepine (n=150) and to phenytoin (n=181) in 2 separate randomized, double-blind trials for treatment of partial or generalized epilepsy.[390,391] Similar efficacy is noted among the agents with lamotrigine better tolerated. Nineteen percent of carbamazepine patients reported rash versus 3% of lamotrigine patients. In the comparative trial with phenytoin, 14% of lamotrigine and 9% of phenytoin patients reported a rash. In the study, the 100 mg per day starting dose for lamotrigine was higher than currently recommended.

lamotrigine (Lamictal) versus valproic acid (Depakene)

Lamotrigine has also been compared to valproic acid as monotherapy in refractory partial epilepsy in a randomized, double-blind trial.[392] Lamotrigine 500 mg proved superior to 1,000 mg of valproic acid with 56% of the 156 patients completing the study versus 20% on valproic acid. Exit criteria were based on worsening seizure activity. Rash was reported by 8% of valproic acid-treated patients and 11% of lamotrigine-treated patients (1 patient with SJS). The lamotrigine titration rate was higher than currently recommended.

levetiracetam (Keppra) versus controlled-release carbamazepine

Adults with 2 or more partial or generalized tonic-clonic seizures in the previous year were randomly assigned to levetiracetam 500 mg twice daily (n=288) or controlled-release carbamazepine 200 mg twice daily (n=291) in a multicenter, double-blind, noninferiority, parallel-group trial.[393] The dosage could be increased incrementally to a maximum of levetiracetam 1,500 mg twice daily or controlled-release carbamazepine 600 mg twice daily. Patients achieving the primary endpoint of a 6-month seizure-free period continued on further treatment for a 6-month maintenance period. At per-protocol analysis, 73% of levetiracetam patients were seizure-free at 6 months and 56.6% were at 1 year versus 72.8% controlled-release carbamazepine patients were seizure-free at 6 months and 58.5% at 1 year. Of all patients achieving 6-month or 1-year remission, 80.1% and 86.0% in the levetiracetam group and 85.4% and 89.3% in the carbamazepine group did so at the lowest dose level. Withdrawal rates for adverse events were 14.4% with levetiracetam and 19.2% with controlled-release carbamazepine.

oxcarbazepine (Trileptal) versus phenytoin (Dilantin) or valproic acid (Depakene)

Oxcarbazepine has been compared to phenytoin and valproic acid for the treatment of either partial or generalized seizures.[394,395,396] The randomized, double-blind studies show the agents have similar seizure control. More phenytoin patients discontinued therapy due to adverse effects. The early discontinuation rates due to adverse events were similar in the valproic acid study.

Oxcarbazepine has also been compared to carbamazepine for generalized tonic-clonic seizures in newly diagnosed patients in a similar double-blind study (n=235).[397] Sixty percent of patients on carbamazepine and 52% of patients on oxcarbazepine remained seizure-free. Twenty-six percent of carbamazepine patients discontinued treatment as compared to 14% of oxcarbazepine patients.

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oxcarbazepine extended-release (Oxtellar XR) versus placebo

A phase 3, multicenter, double-blind, randomized, 3-arm, parallel group, placebo-controlled study evaluated the efficacy of oxcarbazepine ER as adjunctive treatment in 366 adults with refractory partial seizures with secondarily generalized seizures, simple partial seizures, or complex partial seizures.[398,399] The study included an 8-week baseline period, followed by a 4-week titration period and 12-week maintenance period. Patients had a mean of at least 3 recorded partial seizures per 28 days during an 8-week baseline phase, receiving 1 to 3 concomitant antiepileptic drugs. Patients were randomized to receive 1,200 mg daily (n=122), 2,400 mg daily (n=123), or placebo (n=121) as part of adjunctive therapy over a 4-week titration period, followed by a 12-week maintenance phase. The primary efficacy endpoint was the median percent change in seizure frequency between the baseline and treatment (titration plus maintenance period) phase for each oxcarbazepine ER dose compared to placebo for the intent-to-treat population. Median percent reduction in total partial seizure frequency was 42.9% for patients treated with 2,400 mg compared with 28.7% for placebo (p=0.003). The median percent seizure reduction was 38.2% in the 1,200 mg group and 28.4% in the placebo group; however, the difference was not significant (p=0.08). Responder rates, defined as patients experiencing greater than 50% reduction in seizure frequency compared to baseline, were 40.7% for the 2,400 mg group, 36.1% for the 1,200 mg group, and 28.1% for the placebo group. A higher percentage of patients discontinued oxcarbazepine than placebo due to adverse events (23.3% versus 11.6%). The most common adverse events were dizziness, headache, somnolence, diplopia, nausea, and vomiting, occurring more frequently with oxcarbazepine ER than placebo, with a higher percentage in the 2,400 mg group than the 1,200 mg group (69.1% versus 56.6%) respectively. No head-to-head trials were conducted to show efficacy was better than the IR formulation.

pregabalin (Lyrica) versus lamotrigine

A phase 3, double-blind, randomized, multicenter, non-inferiority study compared the efficacy and tolerability of pregabalin and lamotrigine monotherapy in patients with newly diagnosed partial seizures.[400] Patients were titrated to either 75 mg oral pregabalin or 50 mg oral lamotrigine twice daily during a 4-week dose-escalation phase, followed by a 52-week efficacy assessment phase where the dose could be increased as needed to a maximum of 600 mg and 500 mg, respectively. The primary efficacy endpoint was the proportion of patients who remained seizure-free for 6 or more continuous months. Patients (n=660) were randomly assigned to pregabalin or lamotrigine, of whom 622 entered the efficacy assessment phase (314 pregabalin, 308 lamotrigine). Fewer pregabalin patients versus lamotrigine patients became seizure-free for 6 or more continuous months (162 [52%] versus 209 [68%]; difference in proportion, -0.16 [95% CI -0.24 to -0.09]). The overall incidence of adverse events was similar between groups and consistent with that in previous studies; dizziness (55 [17%] versus 45 [14%]), somnolence (29 [9%] versus 14 [4%]), fatigue (27 [8%] versus 19 [6%]), and weight increase (21 [6%] versus 7 [2%]) were numerically more common in the pregabalin group than in the lamotrigine group. The authors concluded that pregabalin has similar tolerability but inferior efficacy to lamotrigine for the treatment of newly diagnosed partial seizures in adults.

pregabalin (Lyrica) versus levetiracetam

A randomized, double-blind, parallel-group non-inferiority study was conducted in adult patients with refractory partial seizures.[401] The efficacy and safety of pregabalin versus levetiracetam as adjunctive therapy was studied. The trial included several phases; a 6-week baseline period, a 4-week dose-

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escalation phase, and a 12-week maintenance phase. The primary endpoint was the proportion of patients with a 50% or greater reduction in 28-day seizure rate during the maintenance phase as compared to baseline. A total of 509 patients were randomized 1:1 to either pregabalin or levetiracetam. With both treatment groups, the proportion of patients meeting the primary endpoint was 0.59 (difference between groups, 0; 95% CI, -0.08 to 0.09). The lower bound of the 95% CI was greater than the prespecified noninferiority margin of -12%; therefore, pregabalin was not inferior to levetiracetam. There was not a statistically significant difference between pregabalin and levetiracetam in the percent change in 28-day seizure rate (median difference, 4.1; 95% CI [-2.6 to 10.9; p=0.3571).

perampanel (Fycompa) versus placebo

The efficacy of perampanel in the treatment of partial-onset seizures, with or without secondary generalized seizures, was established in 3 randomized, double-blind, placebo-controlled, multicenter trials (Studies 1, 2, and 3) involving adult and adolescent patients aged 12 years and older totaling 1,038 patients.[402,403,404,405] Patients enrolled included those who were not adequately controlled on therapy with 1 to 3 concomitant anti-epileptic drugs during and initial 6-week baseline period. During the baseline timeframe, patients were required to have more than 5 seizures in order to be randomized. The baseline period was then followed by an overall treatment period consisting of a 6 week titration phase followed by a 13-week maintenance phase (overall treatment of 19 weeks). Patients included in the 3 trials had a history of epilepsy symptoms with a mean duration of approximately 21 years along with a median baseline seizure frequency that ranged from 9.3 to 14.3 seizures every 28 days. During the 3 trials, greater than 85% of the included patients had treatment regimens consisting of 2 to 3 concomitant anti-epileptic medications with or without concurrent vagal nerve stimulation. Approximately one-half of the patients were taking an anti-epileptic medication that was known to induce the CYP3A4 enzyme (an enzyme important in perampanel metabolism). The presence of these enzyme-inducing medications resulted in significant serum reductions of perampanel concentrations. Each study evaluated the doses administered for placebo and multiple perampanel doses. In the titration phase of all 3 trials, perampanel patients received starting doses of 2 mg once daily, with subsequent increases of 2 mg per day on a weekly basis until the final target dose was achieved. If patients were seen to experience adverse events, they were permitted to have dosage reductions to a level that was previously tolerated. The primary endpoint in all 3 studies was the percent of change in seizure frequency measured over a period of 28 days. Measurements of seizure frequency were evaluated during the treatment period as compared to that seen in the baseline period. The criterion for statistical significance was $p<0.05$. There was a statistically significant decrease in seizure rate observed at doses of 4 mg to 12 mg per day. Notable dose response was seen when the dosage was set at 4 mg to 8 mg per day, (range, -13.7 to -20.1%) with little additional reduction in seizure frequency seen when dosage was increased to 12 mg per day (-13.7%).

topiramate XR (Qudexy XR) versus placebo

The efficacy of topiramate XR as adjunctive treatment in adult patients with partial onset seizures was demonstrated in a double-blind, randomized, parallel-group study in patients with history of partial onset seizures, with or without secondary generalization.[406] Patients (n=249) on a stable dose of 1 to 3 anti-epileptic drugs (AEDs) entered an 8-week baseline period and those who experienced 8 or greater partial onset seizures, with or without secondary generalization, and less than 21 consecutive seizure-free days were randomized to topiramate XR or placebo, administered once daily, along with their

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AEDs. The treatment phase consisted of a 3-week titration period, where a final dose of topiramate XR 200 mg once daily was ultimately achieved in the treatment group, and an 8-week maintenance period. The primary endpoint was the percent reduction in the frequency of partial-onset seizure between baseline and treatment phase. There was a statistically significant decrease in the primary endpoint; the median percent reduction in seizure rate was 39.5% in patients taking topiramate XR compared to 21.7% in patients taking placebo.

topiramate (Topamax) versus phenytoin

A randomized, double-blind, 28-day trial of topiramate 100 mg/day versus phenytoin 300 mg/day (after 1,000 mg loading dose) was conducted in 261 patients with new-onset epilepsy.[407] The primary endpoint was time to seizure, and the primary objective was to establish non-inferiority of topiramate to phenytoin in the risk of seizure. At day 28, the estimated seizure-free rate was 81.1% for topiramate compared to 90.3% for phenytoin. Non-inferiority of topiramate to phenytoin could not be established (hazard ratio [HR], 2; 95% CI, 0.98 to 4.12; p=0.366); phenytoin was not superior to topiramate. A higher percentage of patients discontinued phenytoin compared to topiramate for all reasons (21.1% versus 12.8%) and due to adverse events (13.4% versus 6.8%). The most common treatment-related adverse events in both groups were dizziness, paresthesia, and somnolence.

zonisamide (Zonegran) versus controlled-release carbamazepine

A non-inferiority trial of 538 adults with newly diagnosed epilepsy randomized patients to either zonisamide once daily or carbamazepine twice daily.[408] After treatment initiation and titration phases, patients entered a 26- to 78-week flexible-dosing period, based on response and tolerance to treatment. Once patients were seizure-free for 26 weeks, they began a 26-week maintenance phase. The primary endpoint was the proportion of patients who were seizure-free for 26 weeks or greater. Approximately 79% of patients in the zonisamide group and 84% of patients in the carbamazepine group met the primary endpoint (adjusted absolute treatment difference -4.5%; 95% CI, -12.2 to 3.1). The incidence of treatment-emergent adverse events (TEAEs) was 60% and 62% for the zonisamide and carbamazepine groups, respectively. In the long-term extension, patients continued their randomized treatment with the option to adjust dosing according to tolerability and response.[409] Efficacy assessments included retention rate and proportion of patients who did not have a seizure for greater than or equal to 24 months while safety assessment included TEAEs and laboratory parameters. Nearly 88% and 85% of patients randomized to zonisamide and carbamazepine respectively, completed the study. The incidence of TEAEs was 26.3% for the zonisamide treatment group compared to 19.6% for the carbamazepine treatment group. The most frequently reported TEAEs were decreased weight and appetite, memory impairment, and a decline in hemoglobin levels. The proportion of patients who went without a seizure for greater than or equal to 24 months was similar for each group (zonisamide 32.3% versus carbamazepine 35.2%).

Pertinent Clinical Comparisons for use in Seizure Disorders[410,411,412,413,414,415,416,417,418,419,420,421]

There is evidence from clinical trials that carbamazepine (Tegretol, Tegretol XR, Carbatrol), gabapentin, lamotrigine, oxcarbazepine (Trileptal), topiramate, valproate, and zonisamide are efficacious as monotherapy in newly diagnosed patients with either partial or mixed seizure disorders. Newly diagnosed patients can be initiated on standard therapy with older agents or on 1 of the newer drugs

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mentioned above. For refractory patients with partial seizures, monotherapy with lamotrigine 500 mg per day (on enzyme inducers) is superior to valproic acid 1,000 mg per day. Immediate release oxcarbazepine (2,400 mg per day) and topiramate (1,000 mg per day) are also effective as monotherapy.

In a *post-hoc* analysis, data from 5 comparative, double-blind, single-drug studies to evaluate the efficacy of treatment of patients with partial seizures with oxcarbazepine (Trileptal) versus carbamazepine, phenobarbital, phenytoin (Dilantin, Phenytek), and valproate for approximately 1 year were pooled to investigate same-patient seizure outcome at 6 and 12 months.[422] The main conclusion was that response at 6 months is an excellent predictor of response at 12 months.

For pediatric patients, the pathophysiology of partial seizures is similar to that of adults and will probably respond to the same drugs. However, gabapentin, lamotrigine, oxcarbazepine (Trileptal), and topiramate are the preferred adjunctive therapies in pediatric patients.

Other Indications

High quality, double-blind, comparative trials have not been performed indicated agents in the management of bipolar disorder or migraine.

META-ANALYSES

Seizures

Comparative meta-analyses of anticonvulsants for the treatment of seizure disorders are limited; however, notable comparative meta-analyses have been included in this review.

A meta-analysis including 10 randomized controlled trials compared carbamazepine immediate-release and carbamazepine controlled-release formulations in patients starting monotherapy (1 trial) and patients treated with an IR formulation but experiencing unacceptable adverse events (9 trials).[423] One trial reported a statistically significant difference in fewer seizures with patients prescribed carbamazepine CR than those prescribed an IR formulation. Four trials reported a statistically significant reduction in adverse events with carbamazepine CR compared to carbamazepine IR; no significant difference was found in 4 trials.

A network meta-analysis of 12,391 patients from 36 randomized controlled trials compared 10 antiepileptic drugs (carbamazepine, phenytoin, sodium valproate, phenobarbitone, oxcarbazepine, lamotrigine, gabapentin, topiramate, levetiracetam, and zonisamide) to evaluate the efficacy of the drugs for seizure control when used as monotherapy and the tolerability based on related adverse effects.[424] This review supported the use of carbamazepine, lamotrigine, and levetiracetam as first-line treatment options for partial onset seizures. For patients with generalized tonic-clonic seizures, the review supported the use of sodium valproate, lamotrigine, and levetiracetam as initial treatment options. This determination was made in consideration of efficacy and long term tolerance.

Bipolar Disorder

A systematic review of treatment of bipolar disorder included a total of 583 articles and 913 papers for randomized controlled trials.[425] Findings suggest that lithium is a useful agent in the acute manic and maintenance phase. Both first and second generation antipsychotics are efficacious in the treatment of acute mania. For bipolar depression, quetiapine (Seroquel®) and olanzapine/fluoxetine (Symbyax®) are

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also effective for treating bipolar depression, while olanzapine (Zyprexa®), quetiapine, and aripiprazole (Abilify®) are effective during the maintenance phase. Valproate and carbamazepine have antimanic properties, whereas lamotrigine may be preferably effective in the treatment of depression but not mania.

Migraine

A systematic review evaluated anticonvulsants for effectiveness in the prophylaxis of migraine.[426] All prospective, controlled studies of anticonvulsants in prevention of migraines published through April 2006 were evaluated. Anticonvulsants, considered as a class, reduce migraine frequency by about 1.3 attacks per 28 days compared with placebo, and more than double the number of patients for whom migraine frequency is reduced by ≥ 50% relative to placebo. Valproate derivatives (Depakene, Depakote/ER) and topiramate (Topamax) were better than placebo, whereas clonazepam (Klonopin) and lamotrigine (Lamictal) were not. Gabapentin (Neurontin) was included in the review, but more research needs to be completed.

SUMMARY

Anticonvulsants have very little or no direct comparative data in the treatment of seizures or any other indication. Selection of drugs for epilepsy treatment frequently depends on particular seizure type.

All agents in this review, except succinimides, cannabidiol (Epidiolex), clobazam (Onfi, Sympazan), clonazepam (Klonopin), and rufinamide (Banzel), are FDA-approved to treat partial seizures. The 2018 American Academy of Neurology (AAN) guideline suggests that lamotrigine (Lamictal), levetiracetam (Keppra), and zonisamide (Zonegran) may be considered effective for patients with new-onset focal epilepsy. In adults 60 years of age and older, lamotrigine (Lamictal) should and gabapentin (Neurontin) may be considered for new-onset focal epilepsy.

The succinimides, clonazepam, and the valproic acid derivatives are FDA-approved for absence seizures. According to the updated AAN guidelines, ethosuximide or a valproic acid derivative should be considered before lamotrigine in newly diagnosed childhood absence epilepsy.

For adults and children with Lennox-Gastaut syndrome, AAN recommends lamotrigine and topiramate. Agents that are FDA-approved as adjunct therapy for this indication include clobazam, felbamate, lamotrigine, rufinamide, and topiramate; clonazepam may be used as mono- or adjunctive therapy. Felbamate should be reserved for use if all other options have been exhausted, and the benefits outweigh the risks of aplastic anemia and hepatotoxicity. Cannabidiol (Epidiolex) is FDA-approved for children and adults with Lennox-Gastaut syndrome as well as Dravet syndrome. It has not been addressed in guidelines yet, but may be an option for adjunctive therapy in patients who experience refractory seizures with these conditions.

Vigabatrin (Sabril) is the only anticonvulsant agent in this review that is indicated for the treatment of infantile spasms. For treatment of infantile spasms, AAN recommends low-dose adrenocorticotropic hormone (ACTH) as the treatment of choice; vigabatrin (Sabril) may be useful for short-term treatment.

Diazepam rectal gel is indicated for the management of select, refractory patients on stable regimens of antiepileptic drugs who require intermittent use to control episodes of increased seizure activity.

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While many patients can be maintained on 1 drug, not all are seizure-free. If control is not achieved with 1 drug, an alternative medication should be attempted before others are added to current therapy. The most common reason for treatment failure is noncompliance, which should be addressed prior to or with treatment changes. Serum plasma levels, available with some drugs within this class, may assist in ensuring proper drug exposure and compliance.

Some anticonvulsant agents are also approved for treatment of other neurologic conditions. Those indicated for the management of bipolar disorder include divalproex (Depakote, Depakote ER), carbamazepine extended-release (Equetro), and lamotrigine immediate-release (Lamictal). Divalproex and topiramate (Qudexy XR, Topamax, Trokendi XR) are also indicated for the prevention of migraine headaches. Gabapentin (Neurontin) and pregabalin (Lyrica) are also used to treat neuropathic pain.

Many drug interactions exist for the anticonvulsants, including interactions among adjunctive anticonvulsants. Phenobarbital, phenytoin, primidone (Mysoline), and carbamazepine are potent inducers of CYP 450 and other enzyme systems, which should be taken into account when prescribing these mediations.

Reduced renal function can lead to an accumulation of renally-excreted anticonvulsants, such as gabapentin, topiramate, levetiracetam (Keppra, Keppra XR, Spritam), and pregabalin (Lyrica). Gabapentin (Neurontin), topiramate, and levetiracetam are preferred for treatment of patients with hepatic dysfunction, whereas valproate and felbamate are potentially hepatotoxic and should be avoided in these patients.

Utilization of anticonvulsants in epileptic women who use oral contraceptives, who desire to become pregnant, or who are pregnant requires considerations related to drug interactions and pregnancy risk factors. The elderly population also requires special considerations related to medication selection and dosage due to age-related factors and their utilization of multiple medications for comorbidities.

It is difficult to make distinctions amongst any of these drugs for any FDA-approved indication. There are small amounts of comparative data, but extensive clinical trials between the agents have not been done. Overall, the agents have similar efficacy with the newer drugs generally having fewer serious adverse effects and drug interactions.

Perampanel (Fycompa) is a Schedule III controlled substance, the barbiturates and benzodiazepines are Schedule IV; cannabidiol (Epidiolex), lacosamide (Vimpat), pregabalin (Lyrica), and brivaracetam (Briviact) are Schedule V.

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